COCAINE'S RATE-INCREASING EFFECTS ON SQUIRREL MONKEYS' FIXED-INTERVAL PERFORMANCE: EFFECTS OF REPEATED ADMINISTRATION

By

KEVIN F. SCHAMA

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1992

UNIVERSITY OF FLORIDA LIBRARIES

ACKNOWLEDGMENTS

The author would like to thank Dr. Marc Branch for assistance in preparation of the manuscript, and Marilyn Aldrige, Forrest Files, Dr. Christine Hughes, Dr. Raymond Pitts, Glen Sizemore, Diana Walker, and Troy Zarcone for assistance with experimentation.

TABLE OF CONTENTS

page

ACKNOWLEDGMENTS.................................. ii

ABSTRACT... iv

INTRODUCTION..................................... 1

METHOD... 24

Subjects................................ 24

Apparatus............................... 24

Behavioral Procedure.................... 25

Determination of Acute Drug Effects......... 26

Determination of Chronic Drug Effects....... 29

Data Analysis........................... 29

RESULTS.. 31

DISCUSSION....................................... 85

SUMMARY AND GENERAL CONCLUSIONS.................. 110

REFERENCES....................................... 112

BIOGRAPHICAL SKETCH.............................. 119

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

COCAINE'S RATE-INCREASING EFFECTS ON SQUIRREL-MONKEYS' FIXED-INTERVAL PERFORMANCE: EFFECTS OF REPEATED ADMINISTRATION

By

KEVIN F. SCHAMA

MAY, 1992

Chairman: Dr. Marc N. Branch
Major Department: Psychology

Four food-deprived squirrel monkeys were exposed daily to a fixed-interval schedule of food-pellet delivery. The fixed-interval value was five minutes for three subjects, and eight minutes for the fourth. Cocaine (0.03-1.7 mg/kg) and saline were injected before occasional daily sessions (acute administration). A dose was then chosen for each subject that reliably increased response rates. This dose was administered before each session (chronic administration). During acute administration some doses of cocaine produced substantial overall increases in response rates for three of the subjects, and less so for the remaining subject, who mostly exhibited increases in response rates early in the session and during the middle portion of the intervals. Chronic administration resulted in a reduction of the increases in response rates seen under acute administration for all subjects. The results were discussed in terms of the reinforcement-loss hypothesis, effort reduction, and schedule-induced behavior.

INTRODUCTION

The use of cocaine in the United States began to increase in the 1970s and continued to increase until the middle of the 1980s. The number of current users, or those who reported using cocaine within the last 30 days, rose from 1.6 million in 1977 to 5.8 million in 1985 (Johanson & Fischman, 1989). Difficulties encountered by individuals using cocaine can be related to direct physiological impairment, such as myocardial infarction (Johanson & Fischman, 1989), or behavioral impairment. Behavioral impairment can be characterized in a number of ways, including the direct action of cocaine on behavior such that relationships between behavior and the environment are changed, and more indirect action such that interference with ongoing behavior occurs as a result of behavior required for cocaine use (e.g. behavior involved in procuring the drug). As an example of possible direct behavioral impairment one may consider the effects of cocaine on the operation of motor vehicles and other heavy machinery. As an example of possible indirect impairment one may consider how the time that an individual spends engaging in behavior which is required for cocaine administration, such as obtaining funds and making contacts with sources, may interfere with other behaviors that are important for employment and appropriate interactions with family members. Thus, cocaine's effects as a reinforcer, per se, are not wholly responsible for its classification as a problem drug. Cocaine's effects on other behavior, deemed important by factors relating to individuals and cultures, also are responsible.

There is a long-standing tradition of interpreting learned behavior, both human and nonhuman, in terms of principles of operant and respondent conditioning (Dollard & Miller, 1950; Skinner, 1948; Skinner, 1953; Skinner, 1957). If the use of these principles in describing human learning and performance is valid, then studying the effects of cocaine on ongoing operant and respondent behavior should prove enlightening with respect to the effects of the drug that are considered important in humans. In addition, the effects of repeated cocaine administration should be studied since cocaine users who seek treatment almost invariably use cocaine repeatedly (Johanson & Fischman, 1989). The study of cocaine's effects on operant behavior in non-humans under controlled conditions is desirable not only because it may have generality with respect to humans, but because it provides an objective framework in which reproducible behavior can be observed in individual subjects (Dews, 1958). It is in this overall context that the current research was conducted.

Behavioral effects of repeated cocaine exposure depend on many factors. Early reports indicated that after repeated exposure cocaine produced larger changes in behavior than during initial exposure (i.e., that sensitization occurred). Tatum and Seevers (1929) reported increases in experimenter-observed activity levels of dogs and a monkey following repeated cocaine administration. Downs and Eddy (1932) reported sensitization to cocaine's effects on a number of observed activities and events, including dying. These reports relied on observational methods which were mostly subjective in nature and not easily repeated by others. Using improved methods, Post and Rose (1976), in addition to experimenter observation, employed photocells to measure horizontal and vertical activity in rats. They found that repeated cocaine administration resulted in increased activity levels and stereotypy, whereas repeated saline administration did not. In a literature review Post and Kopanda (1976) noted that sensitization was most often observed when the behaviors and events measured were general activity level, stereotypy, dyskinesias, seizures, hyperthermia, and death.

In contrast to studies reporting sensitization, other research shows that tolerance can develop to cocaine's effects after repeated administration. A number of studies have shown tolerance to cocaine's response-rate-disrupting or error-increasing effects on operant behavior of monkeys

(Branch & Sizemore, 1988; Hughes & Branch, 1991; Woolverton & Kleven, 1988) pigeons (Branch, 1990; Branch & Dearing, 1982; Moore & Thompson, 1978; Schama & Branch, 1989; Thompson, 1977) and rats (Woolverton, Kandel & Schuster, 1978a). Branch and Dearing (1982) pointed out that operant behavior tends to be more sensitive to cocaine's initial effects and that studies of repeated administration have tended to use smaller doses when looking at such behavior. In support of this generalization Branch and Dearing (1982) and Grabowski and Dworkin (1985) have noted that studies reporting sensitization have tended to use larger doses than studies reporting tolerance. There is also direct evidence that the dose of cocaine used may modulate the effects of repeated cocaine administration. In a study by Branch (1990) sensitization occurred to cocaine's response-rate-decreasing effects in one subject during repeated administration. After the repeatedly administered dose was decreased, tolerance was observed.

The temporal relationship between cocaine administration and behavior can also be an important modulator of the effects of cocaine when administered repeatedly. Wilson and Brenkert (1978) noted sensitization to cocaine's anorectic effects in rats when cocaine was given before daily one-hour feeding sessions, but decreased effects (tolerance) when cocaine was administered after the session. In fact, all of the rats receiving cocaine before sessions died, and all receiving cocaine after sessions survived. In a related experiment, Woolverton, Kandel, and Schuster (1978b) studied rats' milk intake under acute and chronic cocaine or d-amphetamine administration. During the repeated-drugging phase some subjects received the drug before each session, and some after. Testing with pre-session administration for both groups showed that tolerance developed to cocaine's initial disruption of milk intake for the group exposed to chronic pre-session administration, and sensitization occurred in the group exposed to chronic post-session administration. These data appear inconsistent with those of Wilson and Brenkert (1978) but, in addition to the type of food used, there are a number of differences between these studies that may account for the different results. Wilson and Brenkert administered 20 mg/kg of cocaine five minutes before sessions, whereas Woolverton et al. administered 16 mg/kg of cocaine 15 min before sessions. Also, the subjects in the study by Wilson and Brenkert had food available only during sessions, whereas the subjects in the study by Woolverton et al. received supplemental feeding outside of sessions.

A number of studies report that tolerance is more likely to occur if a drug's effects are assessed in the same environment in which the repeated administration occurred (Crowell, Hinson, & Siegel, 1981; Krank, Hinson, & Siegel, 1984; Siegel, 1977; Siegel, 1978). In a study by Branch and

Sizemore (1988) the context in which cocaine was repeatedly administered altered its effects. Branch and Sizemore reinforced heterogeneous chains of two to five responses in squirrel monkeys. Under this schedule each trial started with two to five lit keys. Presses on a key consistent with the experimenter-selected sequence resulted in darkening of the key or, at the end of the chain, reinforcer delivery. Presses inconsistent with the sequence resulted in a time out. Certain doses of cocaine initially decreased accuracy. Chronic post-session administration did not result in changes in accuracy, while subsequent chronic pre-session administration, in the same subjects, resulted in tolerance to reduction in accuracy for two of three subjects. It seems, then, that an important determiner of cocaine tolerance is whether or not cocaine is active in the presence of the behavior of interest. Chen (1968) suggested that when an interaction of a drug with behavior is a necessary condition for tolerance, the reduction in the drug's effects should be considered behavioral tolerance. Conversely, when the interaction is not as important, i.e., the drug need not be active when the behavior occurs, the reduction in the drug's effects should be considered physiological tolerance.

Other factors have been implicated as modulators of cocaine tolerance. Hoffman, Branch, and Sizemore (1987) maintained pigeons' keypecking under a multiple schedule in which each of three components arranged reinforcers according to a fixed-ratio (FR) schedule in which the ratio requirement was relatively low, medium, or high, respectively. (FR schedules deliver contingent events after the last of a fixed number of responses.) Rates of responding under the larger-valued schedules were initially more sensitive to cocaine, and less susceptible to tolerance development during chronic administration. Hoffman et al. suggested that the amount of effort required for reinforcer delivery may be a modulator of cocaine tolerance. Hughes and Branch (1991) extended these findings to squirrel monkeys. One confound in these two studies is that between ratio value, or response requirement, and reinforcement rate; larger response requirements resulted in lower reinforcement rates. To examine the effects of reinforcement rate, unconfounded with response requirement, Schama and Branch (1989) studied the effects of acute and chronic cocaine administration on pigeons' responding under a three-component multiple schedule in which each component arranged a fixed-interval (FI) schedule of different length. (FI schedules deliver contingent events immediately following the first response that occurs after a fixed, specified time period.) Values were chosen for the FI schedules so that baseline reinforcement rates would approximate those found in the Hoffman et al. study, thus allowing behavior maintained in the context of different reinforcement rates to be examined independent of response requirement. It was found that cocaine tolerance was not a function of FI value within the parameters studied. Branch (1990) extended these findings to random-ratio (RR) and random-interval (RI) schedules. In this study tolerance was more likely to be a function of schedule value under RR than RI schedules. The results of the studies by Branch (1990) and Schama and Branch (1989) lend support to the hypothesis that response-requirement, independent of reinforcement rate, is an important modulator of cocaine tolerance.

Another modulator of cocaine tolerance may be the degree of stimulus control over responding. Thompson (1977) reinforced pigeons' four-response sequences (chains) on three keys. During the sequence, all keys were lit with a color that was correlated with the next response requirement in the sequence. Keypecks consistent with the designated sequence either advanced the chain or resulted in reinforcer delivery. All other keypecks resulted in a five-second timeout, after which the chain was reinstated at the point at which the error was made. The subjects were studied under "performance" baselines, during which the sequence requirement was the same from session to session, and "learning" baselines, during which the sequence requirement changed from session to session. Cocaine initially increased total errors, decelerated error reduction across the session, and increased pausing. Cocaine also increased perseverative errors, or errors of pecking the same key twice in succession. Chronic administration resulted in tolerance to these effects in both learning and performance conditions, but tolerance was acquired faster under the performance condition. Thompson suggested that tolerance developed more quickly under the performance condition due to stronger stimulus control. Thompson and Moerschbaecher (1979) found the same pattern of effects of acute cocaine and d-amphetamine administration using squirrel monkeys and a multiple-schedule arrangement of learning and performance components. In addition, the drugs were administered during sessions after the sequence contingencies had acquired control of responding in a "learning" component, and no differential effect was found at this point. The authors attributed this to weaker stimulus control or lower reinforcement rates at the beginning of the learning component.

An experiment by Branch and Dearing (1982) also illustrates the effects of stimulus control on cocaine tolerance. They exposed pigeons to a delayed matching-to-sample procedure in which pecks on a lit center key immediately turned off the center keylight and turned on two side keylights after a 0.05-s to 4-s delay. Pecking the side key that was the same color as the center key resulted in reinforcer delivery. The delay values varied within the session. Acute cocaine administration decreased accuracy by generally increasing position and color preferences. Accuracy at the longer delays was more easily disrupted by cocaine. Chronic cocaine administration resulted in tolerance under all delays, but developed more slowly under the longest delay. It is tempting to relate these findings to Thompson's (1977) in that the delay in Branch and Dearing's study may be considered to alter the strength of stimulus control by the center keylight, thus altering cocaine's effects. This interpretation should be viewed with caution, however, since only one of the two subjects in the study by Branch and Dearing displayed more errors at the longest delay value. In addition, Branch and Dearing pointed out that performances that are more sensitive to a drug's initial effects, in this case performance after longer delays, may develop tolerance more slowly because the chronic dose is functionally larger. This assertion is relevant to a number of studies that report less or slower tolerance to a drug's effects on performance which was initially more sensitive (Hoffman, Branch, & Sizemore, 1987; Moore & Thompson, 1978; Thompson, 1977).

Another modulator of cocaine tolerance may be the initial effect that cocaine has on behavior with respect to obtaining reinforcers. In a seminal experiment illustrating the importance of drug-environment interactions, Schuster, Dockens, and Woods (1966) exposed rats to a multiple schedule in which lever-presses were reinforced according to an FI 30-s schedule of food delivery in one component and an interresponse-time-greater-than 30-s (IRT>30-s) schedule in the other component. (IRT>-*t* schedules present contingent events after responses which occur at least *t* seconds from the immediately preceding response.) Schuster et al. noted that the effects of repeated administration of *d*-amphetamine depended on its initial effects on reinforcement rate. In particular, when *d*-amphetamine increased response rates under the IRT schedule or decreased reinforcement rates under the FI schedule tolerance occurred. When *d*-amphetamine increased responding under the FI schedule, tolerance did not occur. Since reinforcement rates decrease when response rates increase on IRT schedules but not FI schedules, Schuster et al. suggested that the initial reinforcement loss produced by a drug may lead to tolerance. This has become known as the reinforcement-loss hypothesis, and has been applied to drugs other than amphetamines, including cocaine.

A number of studies have found reinforcement-loss to be an important factor in tolerance to cocaine's effects. Woolverton, Kandel, and Schuster (1978a) exposed one group of rats to an FR 40 schedule, and another group to an IRT>20-s schedule of food presentation. They found tolerance to cocaine's response-rate-increasing effects in all subjects on the IRT>20-s schedule, and tolerance to cocaine's response-rate-decreasing effects in two of four subjects on the FR 40 schedule. The two subjects which did not show tolerance also showed less initial disruption in reinforcement rates under cocaine. These results are consistent with the reinforcement-loss hypothesis in that tolerance occurred to both cocaine's response-rate-increasing and -decreasing effects when reinforcement rate was initially disrupted. The interpretation of the results of the two subjects that did not show tolerance should be approached with caution, however, since, as Woolverton et al. point out, these subjects were given larger chronic doses.

Another study that supports the reinforcement-loss hypothesis was conducted by Moore and Thompson (1978). These experimenters studied pigeons' pecking on a multiple FR 1 extinction (EXT) schedule in which each keypeck produced food during the FR 1 component, and no food was presented during the EXT component. In addition, there was a mirror in the operant chamber, and pecks on it were recorded. Under non-drug conditions key-pecking predominated during the FR 1 component, and responding on the mirror (labeled aggressive responding) predominated at the beginning of extinction periods. Responding on the mirror was more sensitive than keypecking to rate reductions by acute cocaine administration. During repeated cocaine administration, some tolerance occurred to cocaine's initial reduction in keypecking, but not in responding on the mirror. The results of this experiment are consistent with the reinforcement-loss hypothesis in that reductions in FR responding resulted in reductions in experimenter-arranged reinforcement rates, and reductions in mirror-responding did not.

A related finding was evident in the study by Thompson (1977) described previously in which "learning" and "performance" conditions were compared; responses during error-produced timeouts were recorded. Regardless of whether cocaine initially increased or decreased responding during the timeouts, no tolerance was observed during repeated administration. Because responding during timeouts had no effects on reinforcement rates, the reinforcement-loss hypothesis predicts that tolerance would not develop to drug-induced changes in behavior during the timeouts.

There are exceptions to the reinforcement-loss hypothesis as applied to the stimulant class of drugs. In experiments by Branch (1990), Hoffman, Branch, & Sizemore, (1987), and Hughes & Branch (1991), described earlier, little or no tolerance occurred to cocaine-produced decreases in rates of behavior maintained by relatively large-valued ratio schedules, even though cocaine decreased reinforcement rates. Also, tolerance has been reported when chronic administration occurred under circumstances in which disruption of reinforcement rate was not possible. In the study by Wilson & Brenkert (1978), described previously, tolerance developed to cocaine-produced decreases in rats' food consumption when cocaine was administered after the session, when food was not available.

In addition to these exceptions to the reinforcement-loss hypothesis, the lack of tolerance to d-amphetamine's rate-increasing effects on FI performance reported by Schuster et al. (1966) is not a reliable finding. For example, Tilson and Sparber (1973) studied the effects of acute and chronic d- and l-amphetamine administration on rats' lever-presses maintained by an FI 75-s schedule of food delivery. The drugs initially increased response rates, and tolerance to this effect occurred during daily pre-session administration after four to six days. Another example was produced by Branch (1979) who exposed squirrel monkeys to a three-component multiple FI 5-min schedule in which the first response after five minutes resulted in either food pellet delivery, shock delivery, or the termination of shock delivery (escape). Under the escape procedure shocks which occurred at two-second intervals were scheduled to begin after five minutes. The first response that occurred after five minutes terminated the series of shock deliveries and produced a 30-second time out during which the chamber was darkened. Thus, all shocks could be avoided if responses occurred during the first two seconds after the interval timed out. All three schedules produced response patterns typical of those under FI schedules, which are characterized by little or no responding early in the interval, followed by increased response rates later in the interval. Pre-session administration of cocaine and d-amphetamine, not less than four days apart, increased response rates during all components. During daily pre-session d-amphetamine administration these effects diminished in all components. Dose-effect evaluations revealed that during repeated administration response rates under different doses became more similar to the original non-drug rates, as opposed to a general "shift to the right" in the dose-effect curve due to larger doses coming to increase rates. That is, tolerance developed to both rate-increasing and rate-decreasing effects.

Howell and Morse (1989), by contrast, did not find consistent tolerance to cocaine's response-rate-increasing effects in FI schedules. They exposed squirrel monkeys to an FI 180-s schedule of stimulus-shock termination. In the absence of responding a shock was delivered two seconds after the three-minute interval expired. Responses during this two-second interval canceled shock delivery and presented a three-second change in ambient illumination from red to white followed by 60 s of timeout. The effects of acute cocaine administration were determined using a cumulative-dosing procedure in which cocaine was administered in incremental doses during four successive 10-min periods, which occurred between blocks of FI schedules, during which no scheduled consequences were in effect. The cumulative-dosing procedure allows assessment of the effects of multiple doses of cocaine during one session (Wenger, 1980). Some doses of cocaine initially produced modest increases in response rates. Howell and Morse then administered cocaine chronically by inserting a subcutaneous osmotic pump that infused cocaine continuously for 14 days. Different rates of infusion (0.1, 0.3, and 1.0 mg/kg/h) were examined, in ascending series, during successive chronic-administration phases that were separated by two months. The effects of different doses were determined cumulatively during and after chronic administration. During chronic administration sensitization occurred to cocaine's rate-increasing effects in two subjects at an infusion rate of 0.1 mg/kg/h, and at 0.3 mg/kg/h in the remaining subject. No tolerance to cocaine's rate-increasing effects was found during chronic administration. These results are difficult to interpret, however, because it is unclear with what the effects of doses during chronic administration are to be compared. These dose effects were determined against a background of chronic infusion, and may represent effects of the injected dose added to the dose produced by continuous infusion. (However, Howell and Morse reported no systematic increase or decrease in responding, across subjects, during chronic infusion.) During redetermination of dose effects immediately following chronic administration, one subject showed changes that indicated tolerance after 0.1 mg/kg/h, and another after 0.3 mg/kg/h.

Although they were not designed to examine the question, two other studies relate to the issue of tolerance to the rate-increasing effects of drugs from the stimulant class on behavior maintained by FI schedules. Ksir (1976) evaluated the effects of changing drug conditions on response rates maintained by FI schedules. He reinforced lever-pressing of rats, in two groups, by FI 180-s schedules of food delivery. One group received d-amphetamine before every session for a number of days, and then saline before every session. Another group initially received saline before every session, then d-amphetamine, and then saline again. Ksir reported that after the transition from chronic saline administration to d-amphetamine administration, two of three subjects showed increased responding, as expected. However, during the transition from chronic d-amphetamine administration to saline administration, three of six subjects showed increased responding. Ksir attributed the increased responding when chronic-administration conditions were changed to a general change in the prevailing stimulus conditions, and not to a particular characteristic of d-amphetamine, per se. More important for the current discussion is a suggestion that tolerance may have occurred to d-amphetamine's rate-increasing effects in at least three subjects. Ksir did not report response rates during chronic d-amphetamine administration. However, it would have been difficult for a transition from chronic amphetamine administration to chronic saline administration to produce further rate-increases if the drug's initial rate-increasing effects had persisted. This is circumstantial evidence that tolerance may have occurred to amphetamine's rate-increasing effects.

Schama and Branch's (1989) study was designed to evaluate the effects of acute and chronic cocaine administration on pigeons' responding under a multiple FI FI FI schedule with different interval parameters. Doses which decreased response rates were chosen for chronic administration, although the effects of other doses were determined, allowing a possible inspection of changes in response-rate-increasing effects. As reported by Schama and Branch, acute cocaine administration did not increase overall response rates appreciably, thus leaving little room to see tolerance to this effect. However, inspection of response rates in successive portions the session revealed that for two subjects smaller doses of cocaine produced rate-increases. For one subject the rate-increases occurred during the FI 120-s schedule toward the end of the session. For another subject the cocaine-produced increases occurred during the FI 5-s and FI 30-s schedules toward the end of the session, and during the FI 120-s schedule near the beginning of the session. Tolerance occurred to these effects during chronic administration. This was accompanied by a general shift to the right in some dose-effect curves in that smaller doses that initially increased responding did not increase it as much during chronic administration, and larger doses that initially decreased responding produced increases.

In relation to the reinforcement-loss hypothesis, then, studies which have provided an opportunity to see tolerance to cocaine or d-amphetamine's rate-increasing effects using FI schedules have not provided a consistent picture. Two studies (Howell & Morse, 1989; Schuster et al., 1966) report no tolerance, and two studies (Branch, 1979; Tilson & Sparber, 1973) report tolerance. Two additional studies (Ksir, 1975; Schama & Branch, 1989) indicate that tolerance may have occurred under some circumstances, but cannot be considered as strong support. The presence of different species, maintaining events, schedule values, dosing regimens, and chronic doses across so few studies makes a difficult task of finding useful generalities.

Given that the lack of tolerance to the rate-increasing effects of d-amphetamine on FI schedules found in the study by Schuster et al. (1966) was important for the origination of the reinforcement-loss hypothesis, it is surprising to find so few studies addressing this issue. Although cocaine is well known for its stimulant properties (Johanson & Fischman, 1989), most studies of tolerance to effects of cocaine on operant behavior involve decreases in response rates (e.g., Branch, 1990; Branch & Sizemore, 1988; Hughes & Branch, 1991; Moore & Thompson, 1978; Schama & Branch, 1989; Smith, 1990; Thompson, 1977; Woolverton, Kandel, & Schuster, 1978a; Woolverton & Kleven, 1988). Notable exceptions are studies involving behavior maintained by IRT>t schedules (Woolverton, Kandel, & Schuster, 1978a) and Sidman avoidance schedules (Smith, 1990).

This emphasis on tolerance to response-rate-decreasing effects of cocaine stands in contrast to research examining the effects of acute administration of cocaine and other stimulants. The rate-increasing effects of drugs from the stimulant class have been studied rather extensively under acute administration, particularly with behavior maintained by FI schedules of reinforcement. Perhaps it is the context in which FI schedules became important in Behavioral Pharmacology that resulted in an imbalance between studies of acute and chronic administration. The importance of acute drug effects on behavior maintained under FI schedules was established by Dews (1955) who studied the effects of acute administration of pentobarbital on pigeons' keypecking maintained by FI and FR schedules. He found that pentobarbital produced increases at smaller doses, and decreases at larger doses regardless of schedule type. However, responding on the FI schedule was more sensitive in that smaller doses were required to produce effects. Since the FI schedule produced different patterns and lower rates of responding, it was suggested that an important modulator of pentobarbital's acute effects is the baseline rate of responding. This suggestion became known as the rate-dependency hypothesis (Dews, 1958), and has been extended to other drugs. Basically, the rate-dependency hypothesis states that baseline rates of responding, independent of the instantiating conditions, will determine a drug's acute effects. Because FI schedules produce different rates of responding in different portions of the interval (the FI "scallop"), they gained importance in the rate-dependency literature as a preparation for conveniently assessing drugs' effects on different response rates. Consequently, the effects of acute administration of many drugs, including cocaine, have been well studied.

The concept of rate-dependency is not without its problems, however, both empirical and conceptual. A number of studies have produced results that are incompatible with rate-dependency. Experiments by Carey and Kritkausky (1972) and Laties and Weiss (1966) indicated that low response rates controlled by explicit discriminative stimuli are less likely to be increased by d-amphetamine than comparable rates not under the control of such stimuli. Punishment has also been used to produce different response rates with which the rate-dependent effects of drugs have been examined. Studies by McMillan (1973) and Foree, Moretz, and

McMillan (1973) showed that low rates of responding produced by punishment are increased less than comparably low rates of unpunished responding.

In part, due to constraints by stimulus control and punishment, the fact that rate-dependency may have been better described as rate-convergence in a large number of instances (Byrd, 1979; Ksir, 1981) and other considerations such as the detraction from an analysis of drug effects in terms of behavioral mechanisms (Branch, 1984), the rate-dependency hypothesis has ceased to be a driving force of research in Behavioral Pharmacology. However, it has left in its wake a rather consistent and detailed picture of the effects of acute administration of drugs from the stimulant class on behavior maintained by simple FI schedules. Smaller doses of these drugs tend to increase overall response rates, increase response rates more earlier in the interval, increase response rates less or decrease rates later in the interval, reduce positive acceleration during the FI, and reduce the duration of the time between the beginning of the interval and the start of responding.

Given that the effects of acute administration of small doses of cocaine and other stimulants on FI performance have been well established, it is instructive to examine changes in these effects as a result of repeated daily administration. As discussed above, the few studies conducted so far, when taken as a whole, have produced mixed and/or ambiguous results. Under these conditions it is difficult to make a clear statement about whether the effects of repeated administration of doses of cocaine which increase response rates maintained by FI schedules support or refute the reinforcement-loss hypothesis. An examination of the effects of repeated cocaine administration on more detailed aspects of FI performance may prove useful. In addition, an examination of chronic administration of a dose of cocaine that initially increases response rates would be an important contribution to a tolerance literature which has focused predominantly on the response-rate-decreasing effects of cocaine. The present experiment examined effects of acute and chronic cocaine administration on several aspects of squirrel monkeys' lever-pressing maintained by an FI schedule of food pellet delivery.

METHOD

Subjects

Four experimentally naive squirrel monkeys, three male and one female (544), served. The subjects were maintained at 85% of their initial free-feeding body weights by supplemental feeding approximately 30 min after session termination. The subjects were housed individually with vitamin-enriched water available at all times.

Apparatus

Experimental sessions were conducted in a Plexiglas restraining chair similar in construction to that described by Hake and Azrin (1963). Subjects were restrained at the waist in a sitting position. A response lever (model number E-21-03, Coulbourn Instruments Company, Lehigh Valley, PA) was located on the right side of the Plexiglas panel facing the subjects. Static forces in excess of approximately 30 g (0.29 N) operated a switch attached to the lever, which resulted in a 0.06-s operation (feedback) of a relay attached to the base of the chair and the recording of a response. Three pairs of 28-VDC colored lights were located above the lever in a horizontal row behind the Plexiglas Wall. A Gerbrands model D-1 pellet dispenser could deliver 190-mg banana-flavored pellets (P.J. Noyes Company, Lancaster, NH) into a receptacle positioned to the left of the lever.

During sessions the chair was placed in a ventilated, sound-attenuating enclosure located in a room with white masking noise continuously present. An experiment controller (Walter & Palya, 1986) which arranged contingencies and collected data was located on top of the enclosure. A Gerbrands model C-3 cumulative recorder also was used to monitor responding.

Behavioral Procedure

After initial shaping, lever-pressing was maintained on an FI schedule of food pellet delivery. At the beginning of sessions, two white lights over the lever were turned on. The first lever-press after the programmed interval expired resulted in immediate food pellet delivery. When a pellet was delivered the lights were extinguished for 0.5 s. Two seconds after food pellet delivery a 1-min timeout began during which all lights and programmed contingencies were extinguished. The lights remained on for 2 s after food pellet delivery so that the subjects would not have to grope for the pellet in the dark. At the end of the timeout the two lights over the lever were again turned on and the cycle repeated.

The value of the schedule was increased over five to seven days until the baseline FI value of 5 min was reached. Due to inconsistent response patterning and failure to get increases in response rates after cocaine administration, the baseline FI value was changed to 8 min for Subject 544. Sessions ended after eight reinforcer deliveries for subjects on the FI 5-min schedule and five deliveries for Subject 544. A time limit of 80 min was imposed on the sessions in case of eliminated responding after cocaine, but this was never reached. Sessions were conducted once per day, seven days per week, at about the same time each day for each subject, and began five minutes after the subjects were placed in the chamber.

Determination of Acute Drug Effects

Determination of the effects of acute cocaine administration began after inspection of plots of daily baseline response rates and patterns, judged by examining index of curvature values (Fry, Kelleher, & Cook, 1960), were determined to be stable. Table 1 displays the number of sessions per phase of the experiment for each subject.

Cocaine hydrochloride was dissolved in 0.9% sodium chloride solution. Injections were made into the thigh or calf muscle five minutes before a session began. Injections were administered not less than four days apart. The injection volume was 0.5 ml/kg, and each dose was administered at least twice. Several doses of cocaine, in a descending series (1.7-0.03 mg/kg), and saline were administered. Table 2 shows the number of injections of each dose and saline used to determine dose-effect functions

TABLE 1

NUMBER OF SESSIONS IN EACH PHASE

SUBJECT	PHASE				
	BASELINE	ACUTE	CHRONIC SALINE	CHRONIC COCAINE	CHRONIC SALINE
541	31	94	7	130	11
542	31	138	17	90	18
543	27	112	7	141	16
544	55	147	9	110	9

TABLE 2

NUMBER OF ADMINISTRATIONS

SUBJECT	PHASE	DOSE (MG/KG)							
		CONTROL	SALINE	0.03	0.1	0.3	1.0	1.3	1.7
541	ACUTE	18	4	3	3	3	3	2	---
	CHRONIC	---	4	2	3	15	4	3	---
542	ACUTE	18	3	2	4	5	2	2	---
	CHRONIC	---	3	2	2	2	11	3	---
543	ACUTE	17	3	2	5	4	3	---	---
	CHRONIC	---	2	3	13	5	3	---	---
544	ACUTE	27	2	2	5	8	5	3	4
	CHRONIC	---	4	2	2	2	14	2	2

for each phase and subject. Cocaine concentrations were determined in terms of the salt. Control values were determined by pooling data from sessions that immediately preceded those in which injections were given.

Determination of Chronic Drug Effects

After the effects of acute cocaine administration were determined, a dose of cocaine was chosen that increased response rates. This dose was then administered daily, before each session, after an initial phase of daily pre-session saline administration. The particular doses chosen for chronic administration were 0.3 mg/kg for 541, 1.0 mg/kg for 542, 0.1 mg/kg for 543, and 1.0 mg/kg for 544. After responding under chronic administration became stable, other doses and saline were substituted for the chronic dose at least twice (see Table 2). Substitutions did not occur less than 4 days apart. After the effects of substitutions of different doses were determined during chronic cocaine administration, saline was administered chronically.

Data Analysis

The data recorded during this experiment were response rates during each session, response rates during each interval of each session, number of responses occurring during successive 19ths of the interval (25.3 s for subject 544 and 15.8 s for all others) cumulated across the session, mean index of curvature during each session, mean initial pause during each session, and initial pause during each interval of each session. It was originally planned that responses in 20 segments of the interval would be counted, but due to a programming oversight, the twentieth segment only contained responses after the interval expired. The initial pause was recorded as the time between the initiation of an interval and the first response.

The index of curvature (Fry et al., 1960) is an index of monotonic change in response rates across an interval. Equation 1 is the general formula for computing the index of curvature where R is the total number of responses and _n_ is the total number of segments. The index of curvature computes the difference between the area under a plot of cumulative responses and time, and the area under a hypothetical plot with the same number of responses distributed evenly across the same time span. An index of zero indicates no change in responding across the interval, and negative and positive indexes indicate negative and positive acceleration, respectively.

$$I=\frac{(n-1)R_n-2\sum_{i=1}^{n-1}R_i}{nR_n} \qquad (1)$$

RESULTS

Figure 1 shows cumulative records of responding for all subjects during the acute- and chronic-administration phases after administration of saline and of the dose of cocaine which was used for chronic administration. The record in the upper left of each frame represents responding under non-drug conditions during the acute-administration phase. Responding generally was characterized by pauses at the beginning of the intervals, followed by positive acceleration through the middle of the intervals, and asymptotic rates toward the end of the intervals.

The records in the lower left of each frame represent responding after acute administration of a dose of cocaine that was to be used for chronic administration with each subject. Cocaine increased response rates of Subjects 541, 542, and 544 substantially during most of the session. There was still positive acceleration within the intervals, although asymptotic rates were achieved earlier in the interval, with a consequent reduction in the duration of the period of positive acceleration. For Subjects 542 and 544, cocaine (1.0 mg/kg) reduced responding at the beginning of the session. This resulted in an increase in delay to the first reinforcer for Subject 542. The transition from

Figure 1. Cumulative records of lever-pressing for all subjects after saline (top pair of records in each frame) and cocaine injections during acute-administration (records on the left) and chronic-administration (records on the right) conditions. Deflections of the response pen indicate pellet deliveries. The cumulative record did not run during timeouts. Doses displayed are those that were used for chronic administration. Records were chosen from sessions during which response rates most closely approximated the means reported in Figure 2.

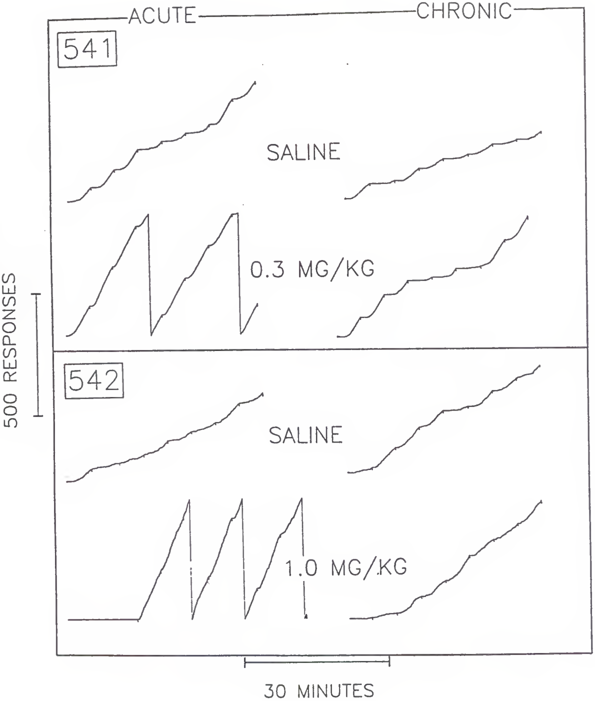
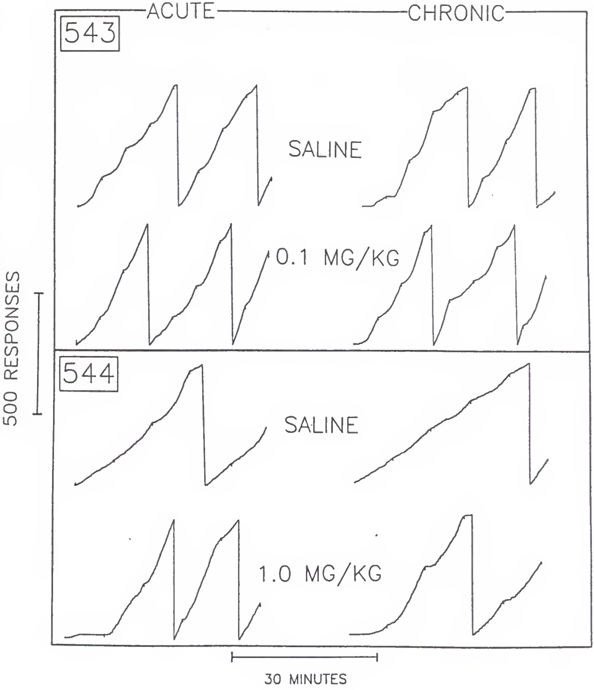

ACUTE
CHRONIC
541
SALINE
0.3 MG/KG
542
SALINE
1.0 MG/KG
500 RESPONSES
30 MINUTES

Figure 1 continued


ACUTE
CHRONIC
543
SALINE
0.1 MG/KG
544
SALINE
1.0 MG/KG
500 RESPONSES
30 MINUTES

depressed responding to accelerated responding was abrupt in these two subjects, especially for Subject 542. Response rates of Subject 543 were not changed by cocaine (0.1 mg/kg) as much as those of the other subjects. Small increases occurred due to earlier asymptotic responding during some of the intervals for this subject.

During daily administration (lower right graph in each frame), the rate-increasing effects of cocaine were diminished in Subjects 541, 542, and 544. In all three subjects this change was characterized by a longer period of positive acceleration, and asymptotic responding achieved later in the interval. In general, these patterns were similar to those after saline injections during the acute-administration phase. For Subject 544, however, there were lower response rates toward the beginning of the intervals during chronic cocaine administration than after saline administration during the acute-administration phase.

During daily administration of cocaine the response-rate-decreasing effects at the beginning of the session in Subjects 542 and 544 were somewhat reduced. Recovery was not complete, but 542's responding increased enough that early session reinforcers were delivered shortly after they became available.

Figure 2 displays mean overall response rates for each subject during acute- and chronic-administration phases as a function of cocaine dose. Acute administration of cocaine produced dose-dependent increases in response rates in all subjects. For Subjects 541 and 543 larger doses of cocaine produced moderate decreases. Subjects 541 and 542 had the lowest non-drug response rates, and also showed the largest increases in overall response rates.

During daily administration the effects of cocaine on overall response rates had a tendency to move toward non-drug control rates, and this was true across doses. The rate-increasing effects of the chronic dose were diminished in Subjects 541, 542, and 544, whereas the effects of 0.1 mg/kg cocaine on Subject 543's overall response rates did not change appreciably during chronic administration. The response-rate-reducing effect of larger doses of cocaine in Subjects 541 and 543 was diminished during the chronic-administration phase.

For Subjects 541 and 544 response rates after saline administration during the chronic-administration phase were lower than during the acute-administration phase, for Subject 542 they were higher, and for subject 543 there was not much change.

To provide a more detailed examination of changes in response rate, Figure 3 shows mean response rates during each interval of the session for all subjects under non-drug, acute-administration, and chronic-administration conditions. The top graph for each subject displays response rates after administration of the dose that was

Figure 2. Mean response rates of each subject as a function of cocaine dose or saline injections (S) during both acute-administration (filled squares) or chronic-administration (open squares) conditions. Control rates (C) were taken from each day immediately prior to an injection during the acute-administration phase. During the chronic-administration phase response rates during exposure to the chronic dose are reported from each day immediately prior to an injection of an alternative dose. The data points represent means of all observations under a particular condition, and the vertical bars on the control points indicate the 99% confidence interval. Note: ordinate ranges change across subjects.

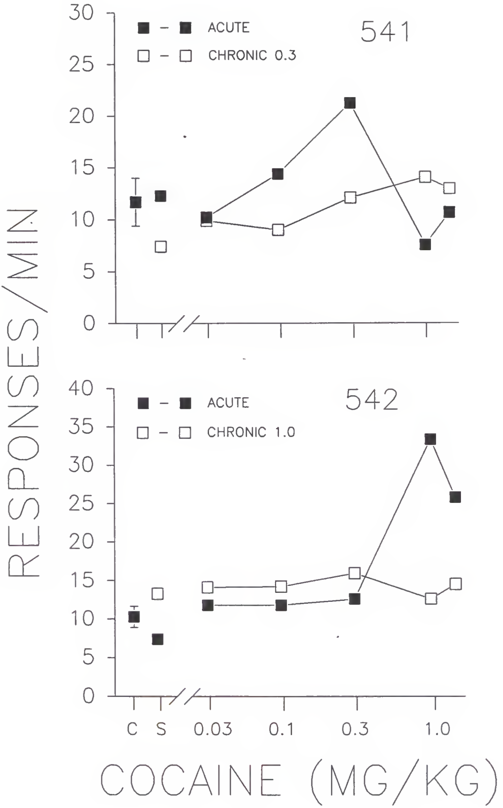
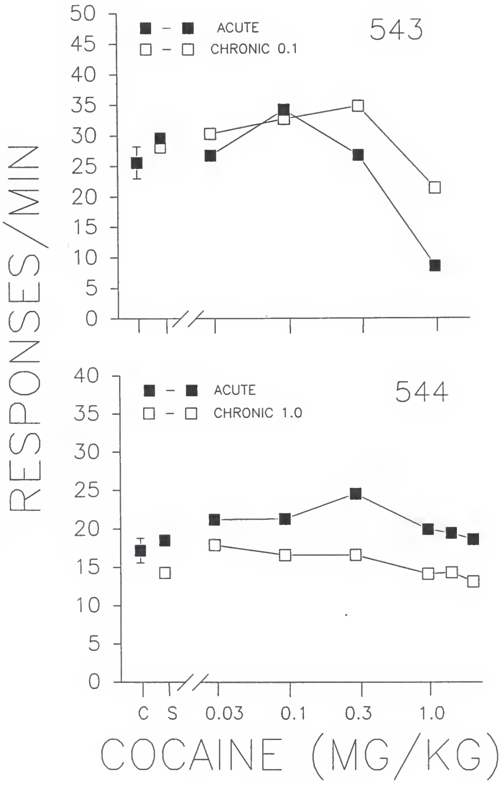

30
25
20
15
10
5
0
■ – ■ ACUTE
□ – □ CHRONIC 0.3
541
40
35
30
25
20
15
10
5
0
■ – ■ ACUTE
□ – □ CHRONIC 1.0
542
RESPONSES/MIN
C
S
0.03
0.1
0.3
1.0
COCAINE (MG/KG)

Figure 2 continued


RESPONSES/MIN
543
■ – ■ ACUTE
□ – □ CHRONIC 0.1
50
45
40
35
30
25
20
15
10
5
0
544
■ – ■ ACUTE
□ – □ CHRONIC 1.0
40
35
30
25
20
15
10
5
0
C
S
0.03
0.1
0.3
1.0
COCAINE (MG/KG)

used for chronic administration in that subject, and the lower graphs present data from all larger doses studied. Under non-drug conditions, there was a small tendency for response rates to increase across each session in Subjects 541, 542, and 543. Acutely, 0.3 mg/kg cocaine increased mean response rates during every interval for Subject 541. Larger doses produced decreases early in the session, followed by smaller increases, or no increases at all, later in the session. Acutely, cocaine decreased Subject 542's response rates during the first interval of the session, and increased rates in all others. This was true for the dose used for chronic administration, and the larger dose studied. Mean response rates after acute 0.1 mg/kg cocaine administration were higher during all intervals of the session for 543, but relatively large increases were seen only during the first three intervals. As the dose increased, response rate-decreases were observed, particularly early in the session, and the decreases lasted for more intervals of the session as dose increased. Subject 544's overall response rates were reduced during the first interval, and increased during almost all of the remaining intervals. This was true for the dose used for chronic administration, and all larger doses studied.

During daily administration the effects of the chronic dose of cocaine were diminished during all of the intervals where acute administration produced increased response rates

Figure 3. Mean response rates for each subject during successive intervals of the session under control (solid bars), acute-administration (open bars), and chronic-administration (cross-hatched bars) conditions. The doses represented are those that were used for chronic administration in each subject and all larger doses. Control data were taken from each session immediately prior to all injections during the acute-administration phase. The bars indicate 99% confidence intervals.

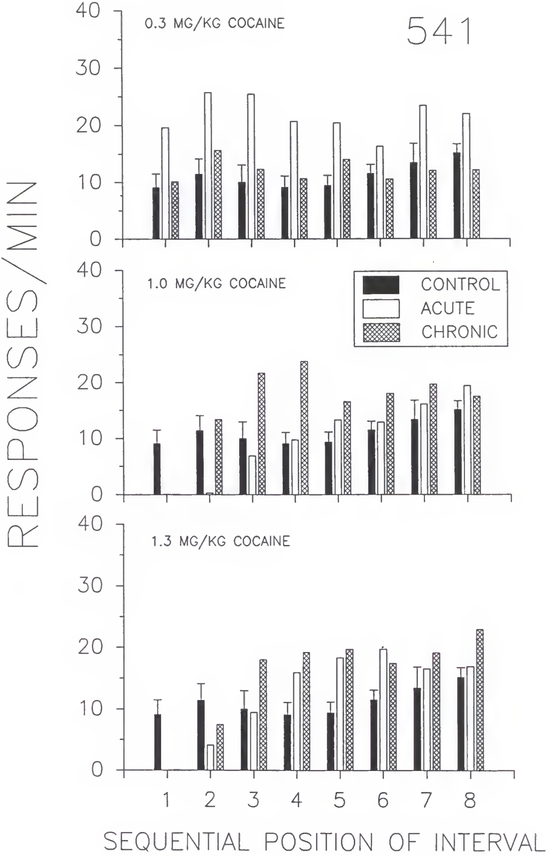

541
RESPONSES/MIN
0.3 MG/KG COCAINE
1.0 MG/KG COCAINE
1.3 MG/KG COCAINE
CONTROL
ACUTE
CHRONIC
0
10
20
30
40
1
2
3
4
5
6
7
8
SEQUENTIAL POSITION OF INTERVAL

Figure 3 continued

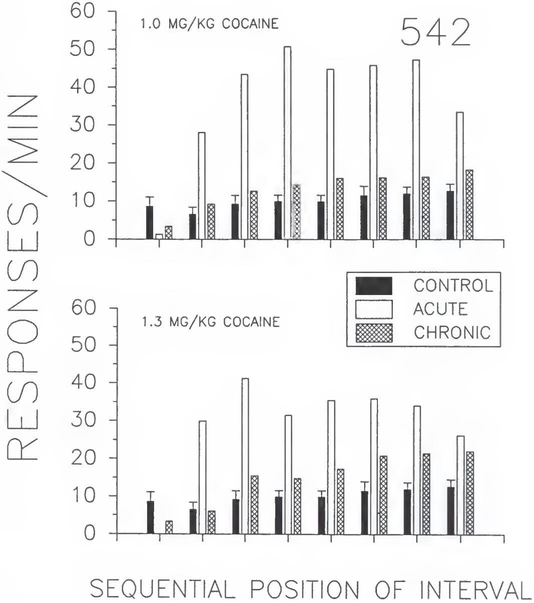

542
1.0 MG/KG COCAINE
1.3 MG/KG COCAINE
0
10
20
30
40
50
60
RESPONSES/MIN
SEQUENTIAL POSITION OF INTERVAL
CONTROL
ACUTE
CHRONIC

Figure 3 continued

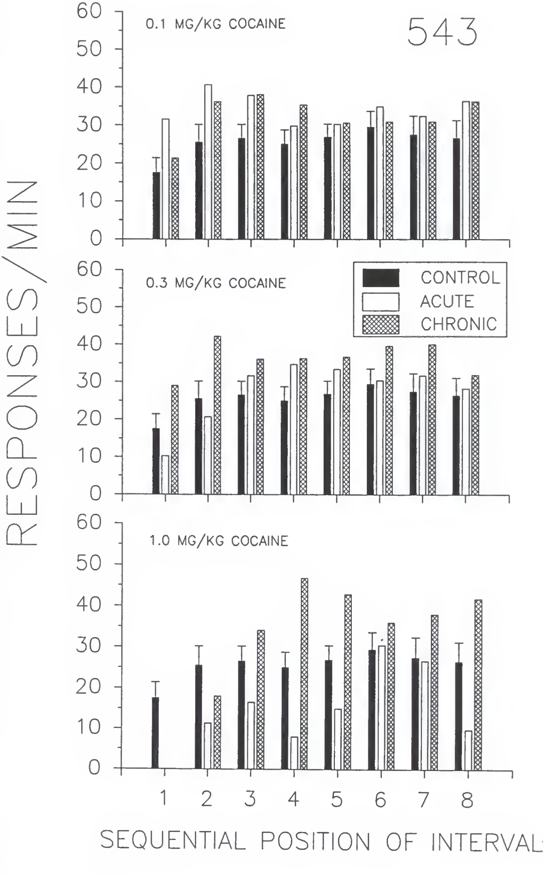
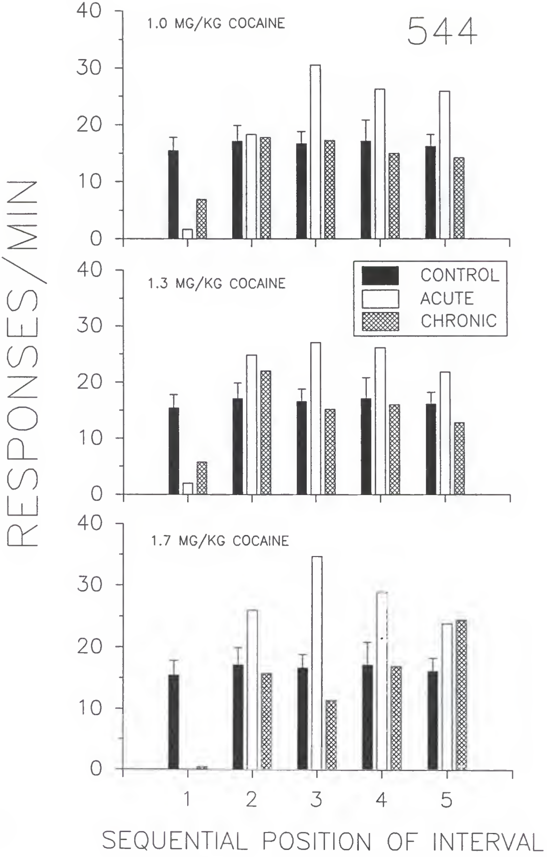

543
RESPONSES/MIN
0.1 MG/KG COCAINE
0.3 MG/KG COCAINE
1.0 MG/KG COCAINE
CONTROL
ACUTE
CHRONIC
0
10
20
30
40
50
60
1
2
3
4
5
6
7
8
SEQUENTIAL POSITION OF INTERVAL

Figure 3 continued


544
1.0 MG/KG COCAINE
1.3 MG/KG COCAINE
1.7 MG/KG COCAINE
CONTROL
ACUTE
CHRONIC
RESPONSES/MIN
SEQUENTIAL POSITION OF INTERVAL
0
10
20
30
40
1
2
3
4
5

in Subjects 541, 542, and 544. Reduction in the response-rate-increasing effects of the chronic dose of cocaine occurred fully during the first interval, partially during the second, and not at all during the third and last intervals for Subject 543. There was only partial recovery from the response-rate-reducing effects of cocaine for Subjects 541, 542, and 544. For Subjects 542 and 544, the response-rate-increasing effects of the larger doses of cocaine were generally diminished during chronic administration. For Subjects 541 and 543, larger doses during chronic administration increased response rates, relative to control rates, during some of the intervals where rates had been decreased or relatively unaffected following acute administration.

Figure 4 shows mean number of responses during successive 19ths of the FI, accumulated across the session, for each subject under non-drug, acute-administration, and chronic-administration conditions. The top graph for each subject represents response rates after administration of the dose that was used for chronic administration in that subject, and the lower graphs present data from all larger doses studied. Under non-drug conditions there was a general increase in mean responding across the interval for all subjects. An exception for Subjects 542, 543, and 544 is that the number of responses during the first segment was larger than the immediately following segments. The dose of

Figure 4. Mean number of responses per session of each subject during each of 19 equal segments of the fixed-interval during control (filled triangles), acute-administration (filled squares), and chronic-administration (open squares) conditions. The doses represented are those that were used for chronic administration in each subject and all larger doses. Control data were taken from each session immediately prior to all injections during the acute-administration phase. The duration of each segment is 25.3 s for subject 544, and 15.8 s for all others. The dotted lines follow the 99% confidence intervals for the control points. Note: ordinate ranges change across subjects.

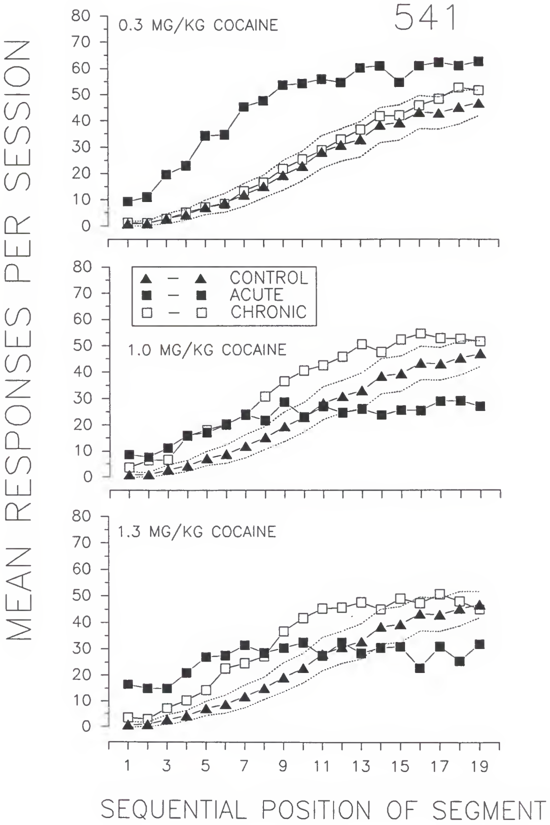

541
0.3 MG/KG COCAINE
1.0 MG/KG COCAINE
1.3 MG/KG COCAINE
▲ – ▲ CONTROL
■ – ■ ACUTE
□ – □ CHRONIC
MEAN RESPONSES PER SESSION
SEQUENTIAL POSITION OF SEGMENT
0
10
20
30
40
50
60
70
80
1
3
5
7
9
11
13
15
17
19

Figure 4 continued

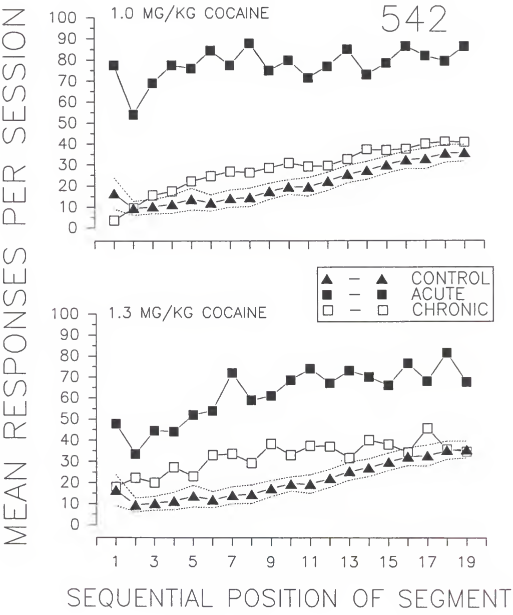

1.0 MG/KG COCAINE
542
1.3 MG/KG COCAINE
MEAN RESPONSES PER SESSION
100
90
80
70
60
50
40
30
20
10
0
▲ — ▲ CONTROL
■ — ■ ACUTE
□ — □ CHRONIC
1
3
5
7
9
11
13
15
17
19
SEQUENTIAL POSITION OF SEGMENT

Figure 4 continued

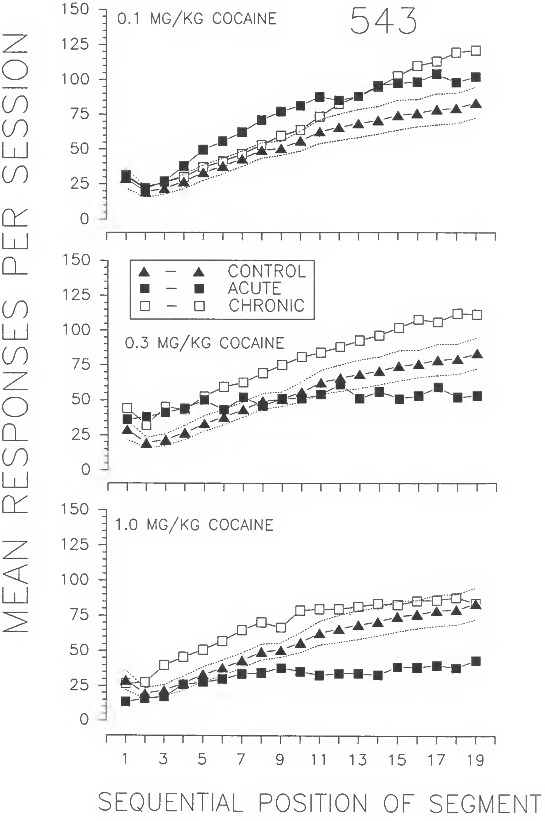
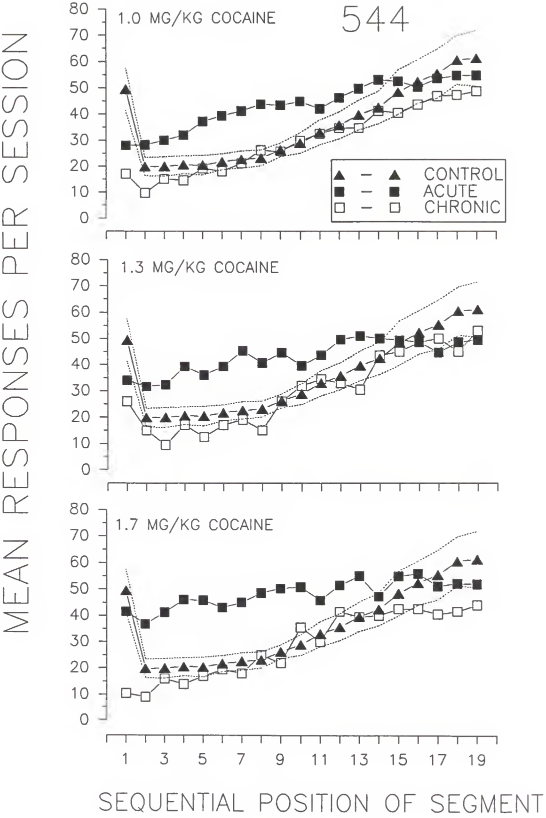

543
MEAN RESPONSES PER SESSION
0.1 MG/KG COCAINE
0.3 MG/KG COCAINE
1.0 MG/KG COCAINE
▲ – ▲ CONTROL
■ – ■ ACUTE
□ – □ CHRONIC
0
25
50
75
100
125
150
1
3
5
7
9
11
13
15
17
19
SEQUENTIAL POSITION OF SEGMENT

Figure 4 continued


MEAN RESPONSES PER SESSION
1.0 MG/KG COCAINE
544
1.3 MG/KG COCAINE
1.7 MG/KG COCAINE
▲ – ▲ CONTROL
■ – ■ ACUTE
□ – □ CHRONIC
0
10
20
30
40
50
60
70
80
1
3
5
7
9
11
13
15
17
19
SEQUENTIAL POSITION OF SEGMENT

cocaine used for chronic administration initially increased response rates during some portion of the intervals in all subjects, with responding during the middle segments increasing the most for Subjects 541, 543, and 544. For Subjects 541, 543, and 544 larger doses tended to make responding more constant across the interval, either by increasing responding early in the interval more, by decreasing responding later in the interval more, or both.

During daily administration number-of-response-increasing effects of both the chronic dose and larger doses were diminished in Subjects 542 and 544. For Subject 541 during chronic administration, the number-of-response-increasing effects of the chronic dose were diminished, but changes in the effects of larger doses were more complicated. In general, administration of these doses during the chronic-administration phase produced smaller increases in responding early in the interval after 1.3 mg/kg cocaine injections, and smaller decreases in responding later in the interval after 1.0 and 1.3 mg/kg cocaine injections. However, during the middle portion of the interval response rates were increased by these doses, relative to control values. Relative to the effects of acute administration of the chronic dose of cocaine, Subject 543's responding was diminished during the middle of the interval, and augmented toward the end of the interval. During chronic administration, larger doses were more likely to produce increases in responding during certain portions of the interval, relative to control values, whereas during acute administration they were more likely to produce decreases.

Figure 5 shows the index of curvature for all subjects as a function of cocaine dose during acute- and chronic-administration phases. Cocaine initially produced dose-dependent decreases in the index of curvature for all subjects. During chronic administration this effect was reduced in Subjects 541, 542, and 544, whereas for subject 543 there was an increase in the index of curvature after all doses, and after saline.

Figure 6 shows overall session means of initial pause duration for each subject as a function of cocaine dose during acute- and chronic-administration phases. Cocaine initially produced dose-dependent increases in initial pause duration in Subjects 542, 543, and 544. For Subject 541 there were decreases in initial pause duration after 0.3 mg/kg cocaine injections, and no appreciable overall effect at other doses. Chronic administration resulted in little change in the relation between pause durations and dose of cocaine for Subjects 542, 543, and 544. The pause-duration-reduction effect of cocaine in Subject 541 was eliminated during chronic administration.

Figure 7 shows mean initial pause duration for each subject in each interval of the session under control,

Figure 5. Mean index of curvature for each subject as a function of cocaine dose or saline injections (S) during both acute-administration (filled squares) or chronic-administration (open squares) conditons. Conventions are as in Figure 2.

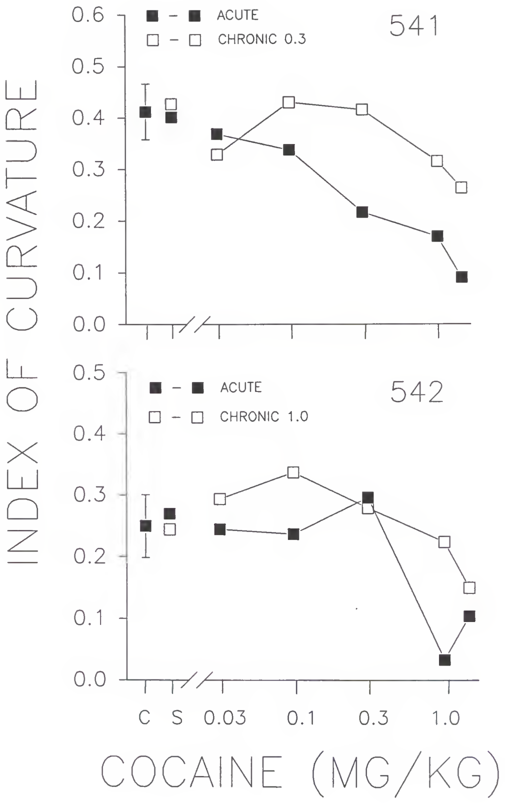

■ – ■ ACUTE
□ – □ CHRONIC 0.3
541
■ – ■ ACUTE
□ – □ CHRONIC 1.0
542
INDEX OF CURVATURE
0.6
0.5
0.4
0.3
0.2
0.1
0.0
C
S
0.03
0.1
0.3
1.0
COCAINE (MG/KG)

Figure 5 continued

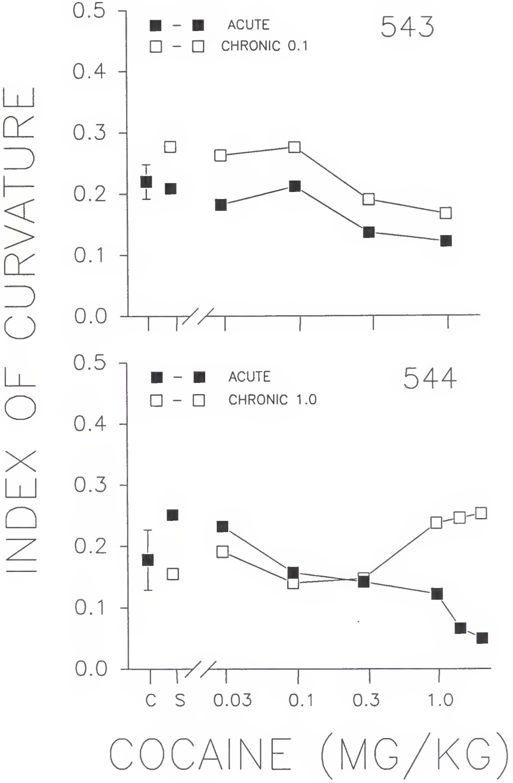

INDEX OF CURVATURE
0.5
0.4
0.3
0.2
0.1
0.0
ACUTE
CHRONIC 0.1
543
0.5
0.4
0.3
0.2
0.1
0.0
ACUTE
CHRONIC 1.0
544
C
S
0.03
0.1
0.3
1.0
COCAINE (MG/KG)

Figure 6. Mean initial pause for each subject as a function of cocaine dose or saline injections (S) during both acute-administration (filled squares) or chronic-administration (open squares) conditions. Conventions are as in Figure 2.

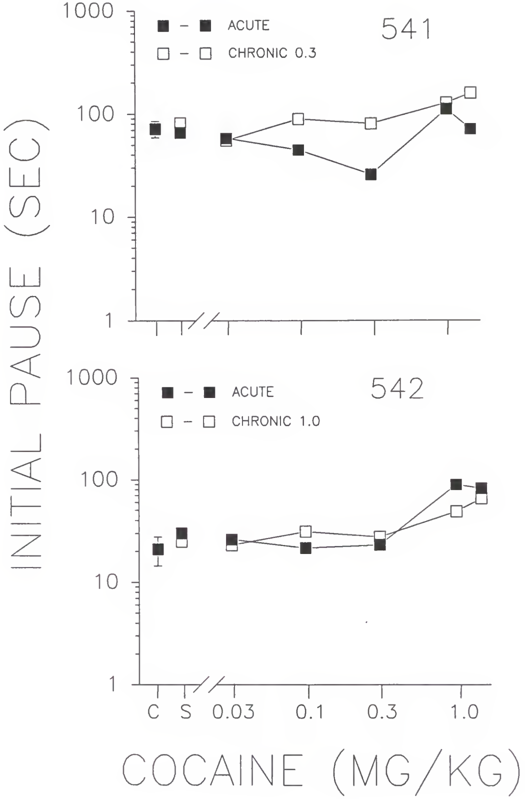
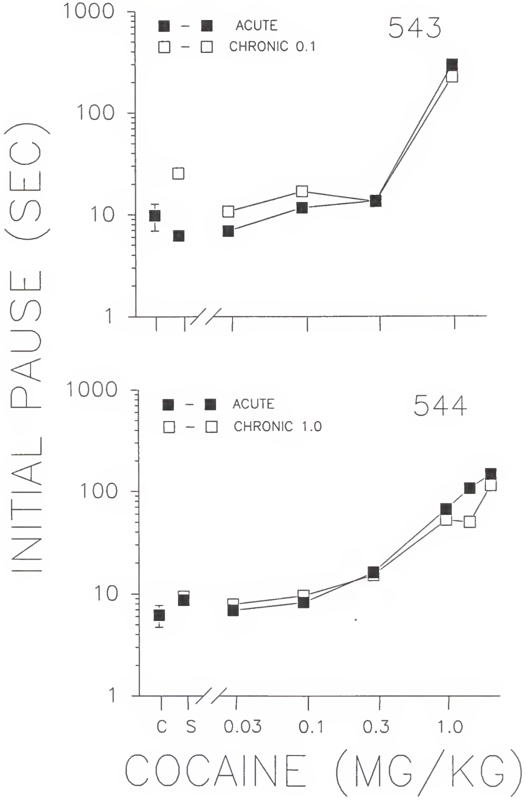

INITIAL PAUSE (SEC)
1000
100
10
1
■ – ■ ACUTE
□ – □ CHRONIC 0.3
541
■ – ■ ACUTE
□ – □ CHRONIC 1.0
542
C
S
0.03
0.1
0.3
1.0
COCAINE (MG/KG)

Figure 6 continued


INITIAL PAUSE (SEC)
1000
100
10
1
■ – ■ ACUTE
□ – □ CHRONIC 0.1
543
■ – ■ ACUTE
□ – □ CHRONIC 1.0
544
C
S
0.03
0.1
0.3
1.0
COCAINE (MG/KG)

acute-administration, and chronic-administration conditions. The top graph for each subject represents response rates after administration of the dose that was used for chronic administration in that subject, and the lower graphs present data from all larger doses studied. Cocaine (0.3 mg/kg) initially produced decreases in pausing of Subject 541 during all intervals of the session. Larger doses produced increases early in the session, and decreases later. During repeated administration, the decreases in pause duration after each dose were diminished, but the increases were not.

Acute cocaine administration (1.0 mg/kg) increased 542's pause duration during the first interval of the session, and tended to decrease pause duration in other intervals. This was true for the larger dose, too. During chronic administration, these doses of cocaine did not increase the pause duration in the first interval as much as it did following acute administration, and no longer decreased the pause duration in any of the subsequent intervals, relative to control data.

Cocaine (0.1 and 0.3 mg/kg) only appreciably increased 543's pause duration during some of the early intervals of the session. During all other intervals there was little or no consistent effect of cocaine. The largest dose of cocaine studied with this subject (1.0 mg/kg) produced substantial increases in pause duration that diminished as the session progressed. During chronic administration,

Figure 7. Mean initial pause for each subject during successive intervals of the session under non-drug (solid bars), acute-administration (open bars), and chronic-administration (cross-hatched bars) conditions. Conventions are as in Figure 3.

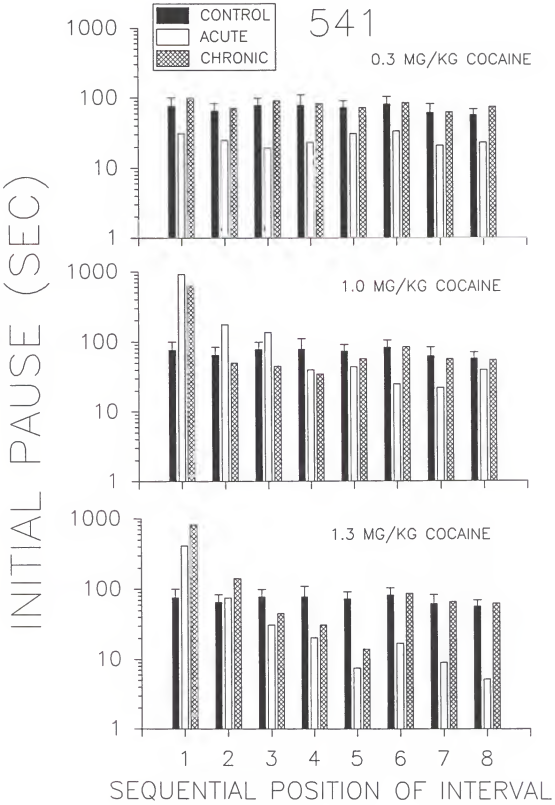

CONTROL
ACUTE
CHRONIC
541
0.3 MG/KG COCAINE
1.0 MG/KG COCAINE
1.3 MG/KG COCAINE
1000
100
10
1
INITIAL PAUSE (SEC)
1
2
3
4
5
6
7
8
SEQUENTIAL POSITION OF INTERVAL

Figure 7 continued

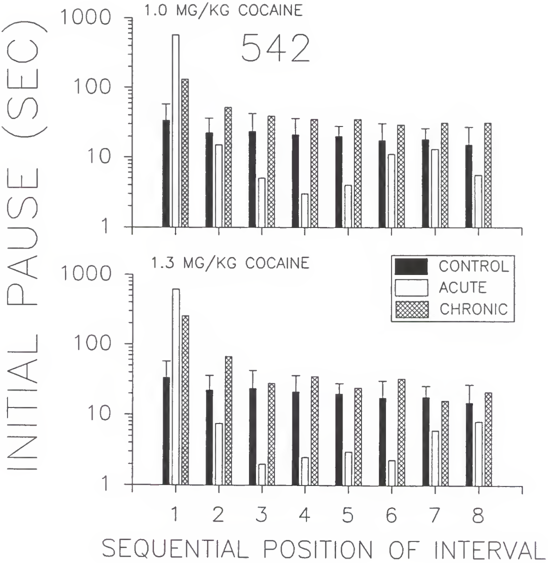

1.0 MG/KG COCAINE
542
1.3 MG/KG COCAINE
CONTROL
ACUTE
CHRONIC
INITIAL PAUSE (SEC)
1000
100
10
1
1000
100
10
1
1
2
3
4
5
6
7
8
SEQUENTIAL POSITION OF INTERVAL

Figure 7 continued

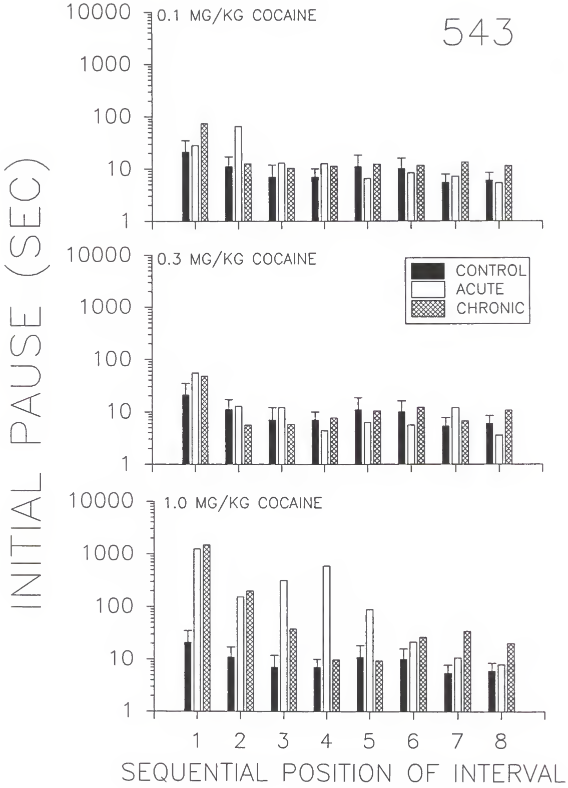
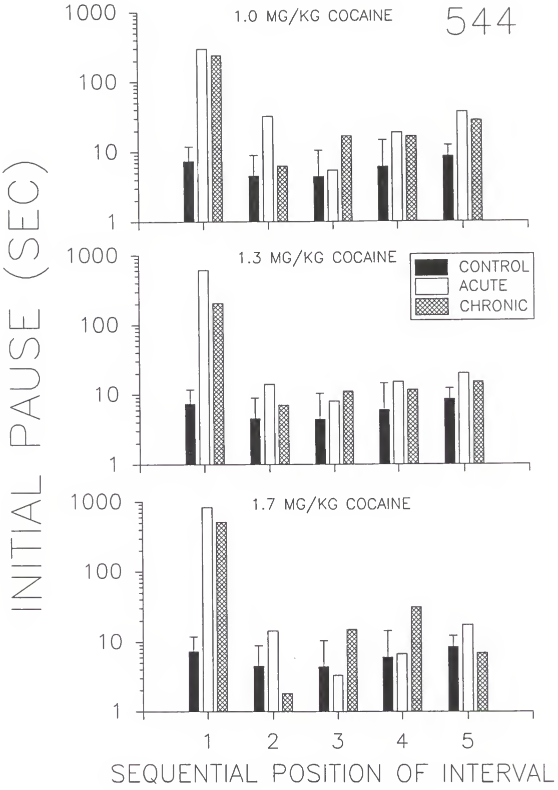

543
INITIAL PAUSE (SEC)
10000
1000
100
10
1
0.1 MG/KG COCAINE
0.3 MG/KG COCAINE
1.0 MG/KG COCAINE
CONTROL
ACUTE
CHRONIC
1
2
3
4
5
6
7
8
SEQUENTIAL POSITION OF INTERVAL

Figure 7 continued


1.0 MG/KG COCAINE
544
1.3 MG/KG COCAINE
1.7 MG/KG COCAINE
CONTROL
ACUTE
CHRONIC
1000
100
10
1
INITIAL PAUSE (SEC)
1
2
3
4
5
SEQUENTIAL POSITION OF INTERVAL

there were no systematic changes in pause duration after 0.1 or 0.3 mg/kg. In addition, during the chronic-administration phase, 1.0 mg\kg cocaine injections continued to increase pause duration during the first two intervals, but increased it less, or not at all, during intervals 3, 4, and 5.

Subject 544's initial pause duration under non-drug conditions was shorter than other subjects'. Cocaine, at the doses shown, tended to increase initial pause duration more in earlier than in later intervals, and larger doses produced longer pause durations in the first interval. This effect was reduced in the second interval during chronic administration, and during the first interval after 1.3 mg/kg cocaine administration.

Figure 8 shows the number of responses during the 7th segment of the interval, cumulated across sessions, for each session of both chronic saline-administration phases, and initial sessions of the chronic cocaine-administration phase. An exception, due to lost data, is that only the last four of the seven sessions of initial chronic saline-administration phase are shown for Subject 541. The 7th segment was chosen because the responding of all subjects was increased during this segment after acute administration of the dose used for chronic administration. Data are shown from the chronic cocaine-administration condition up to the first session in which a dose substitution occurred.

Figure 8. Mean number of responses during the 7th segment plotted across the first sessions during the chronic-administration cocaine phase and the preceding and subsequent chronic saline phases.

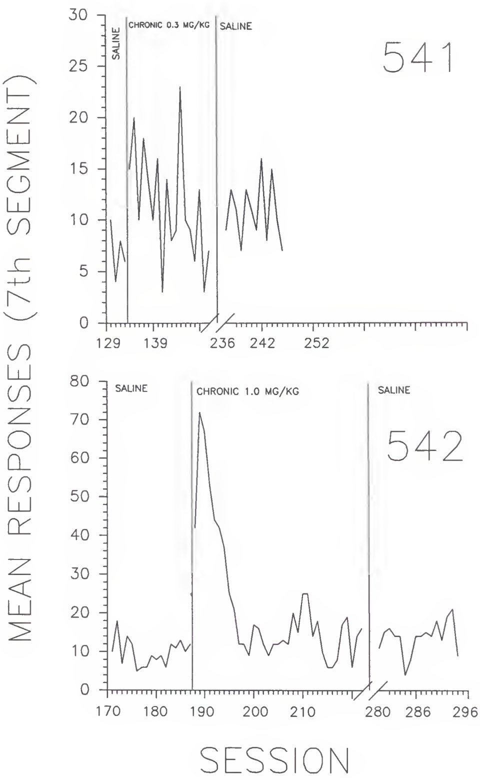
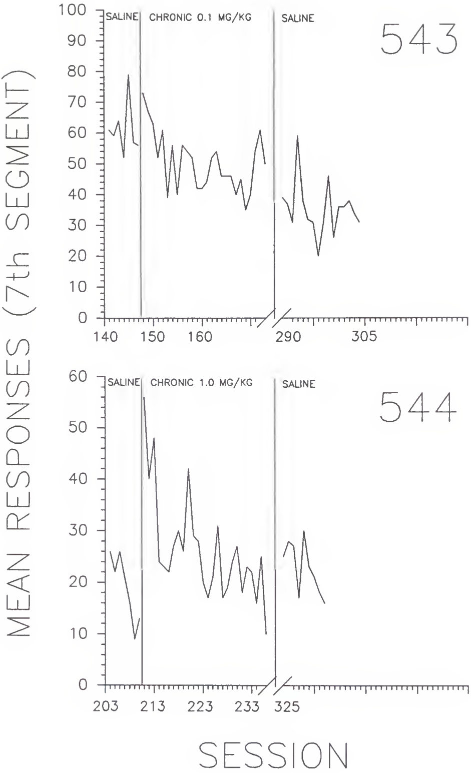

MEAN RESPONSES (7th SEGMENT)
SESSION
30
25
20
15
10
5
0
SALINE
CHRONIC 0.3 MG/KG
SALINE
541
129
139
236
242
252
80
70
60
50
40
30
20
10
0
SALINE
CHRONIC 1.0 MG/KG
SALINE
542
170
180
190
200
210
280
286
296

Figure 8 continued


MEAN RESPONSES (7th SEGMENT)
SESSION
543
SALINE
CHRONIC 0.1 MG/KG
SALINE
100
90
80
70
60
50
40
30
20
10
0
140
150
160
290
305
544
SALINE
CHRONIC 1.0 MG/KG
SALINE
60
50
40
30
20
10
0
203
213
223
233
325

Therefore, the number of sessions shown from this condition differ for each subject. Cocaine initially produced increases in responding in Subjects 541, 542, and 544, and this effect diminished over sessions. For Subject 543, responding during the initial chronic saline-administration phase was elevated relative to mean responding during the acute-administration phase (cf. Figure 4 which shows an average control number of about 42 responses during segment 7). Subsequent cocaine administration had no initial effect on responding relative to the previous chronic saline-administration phase. Responding decreased, however, during the initial sessions of the chronic cocaine-administration phase for Subject 543, approaching levels seen under control conditions (cf. Figure 4). Responding during the final chronic saline-administration phase was not much different than during the chronic cocaine-administration phase for Subjects 541, 542, and 544, whereas for Subject 543 responding was somewhat less.

DISCUSSION

During the present experiment, in almost every instance where response rates were increased after acute cocaine injections, tolerance developed to this effect during repeated daily pre-session administration. In particular, tolerance occurred to cocaine's overall response-rate-increasing effects for Subject 541, 542, and 544 (Figure 2). For Subjects 542 and 544 tolerance occurred to cocaine's effects, at the chronic dose and all larger doses studied, in all intervals of the session and segments of intervals where it increased response rates when administered acutely. For Subjects 541 and 543, tolerance during certain intervals of the session and segments of intervals occurred primarily to the rate-increasing effects of the chronic dose. Little tolerance, and in fact some sensitization with respect to rate-increases, was observed at larger doses in these two subjects. This sensitization can be characterized as part of a general shift in the initial effects of smaller doses to larger ones. In addition, tolerance developed to cocaine's initial decrease of index of curvature in all subjects and to decreases in the initial pause in Subjects 541 and 542.

Several important aspects of responding that are not evident in the overall session means are revealed by the inspection of behavior across the session (Figures 3 and 7). For Subject 542 the mean effects of cocaine on initial pause were not accurately descriptive of the effects of 1.0 or 1.3 mg/kg cocaine. Cocaine increased the pause during the first interval of the session, and decreased pause duration during all others. Where cocaine decreased pause duration, tolerance developed to this effect. Similarly, the degrees of increase in overall response rates indicated for Subject 542 at 1.0 and 1.3 mg/kg doses and for Subject 544 at 1.0, 1.3, and 1.7 mg/kg doses (Figure 2), after acute cocaine administration, underrepresent the increase that occurred during certain portions of the session. This is, in part, due to cocaine's rate-decreasing effects early in the session for these two subjects. Also, inspection of mean response rates during each interval for Subject 543 showed that initial rate-increases and subsequent tolerance were more pronounced at the beginning of the session.

Recording of changes in behavior across segments of the interval after acute and chronic cocaine administration (Figure 4) also revealed important features of responding that were not seen by examining overall response rates (Figure 2) alone. One of the more striking differences is that, for Subject 543, although overall session mean response rates showed very little change during chronic administration, inspection of responding across the segments revealed that chronic administration produced tolerance to rate-increases early in the interval even though these increases, too, had no effect on reinforcement frequency.

For Subjects 541 and 543, inspection of responding during individual intervals and segments of the intervals revealed that during chronic administration doses of cocaine larger than the chronic dose produced increases in responding, relative to pre-chronic control levels, more often than they did during acute administration. Together with the finding of tolerance to the rate-increasing effects of the chronic dose in these subjects, this indicates that the general dose-effect function "shifted" toward larger doses. In other words, during chronic administration in these two subjects, a particular dose of cocaine produced effects more similar to those of smaller doses during acute administration. These data stand in contrast to those produced by Subjects 542 and 544. For these subjects chronic cocaine administration caused the performance under the chronic dose and larger doses studied to more resemble control performances. This can be characterized as a general "flattening" of the dose-effect function. One factor stands out as a possible contributor to these differences. The chronic dose chosen for study was smaller for Subjects 541 and 543. This indicates that these two subjects' behavior was initially more sensitive to cocaine's rate-increasing effects. It is therefore possible that, during chronic administration, the largest doses studied with these two subjects were within the range that would produce increases. Since the behavior of Subjects 542 and 544 was initially less sensitive to rate-increases, it is possible that a shift in the dose-effect function occurred, but the larger doses studied were not large enough to produce rate-increases after tolerance occurred during chronic administration.

In the present experiment the rate-increasing effects of cocaine diminished over 10-12 sessions for Subjects 541, 542, and 544 (cf. Figure 8). This may be compared to the results of Tilson and Sparber (1973) who reported that tolerance to *d*-amphetamine's effects on FI-maintained lever-pressing by rats occurred in four to six sessions. In the present experiment, response rates during the initial portions of the chronic cocaine-administration phase decreased for Subject 543. In this subject, however, cocaine did not initially produce a substantial increase in response rates over rates during the previous chronic-saline-administration phase. Perhaps this occurred because response rates during the chronic-saline-administration phase were elevated relative to rates during control sessions.

In the present experiment, baseline response rates and patterns were typical of squirrel monkeys' performance under

FI schedules of food presentation (Branch, 1979; Kelleher & Morse, 1964; Spealman, Goldberg, Kelleher, Goldberg, & Charlton, 1977). The effects of acute administration of cocaine also were consistent with research that investigated the effects of stimulant-class drugs on performance under FI schedules. Cocaine increased overall response rates (cf. Branch & Gollub, 1974; Byrd, 1979; Howell, Byrd, & Marr, 1986; Kelleher & Morse, 1964; McAuley & Leslie, 1986; McMillan, 1968; McMillan & Healey, 1976; Spealman et al., 1977), tended to increase responding more during the middle portion of the interval (cf. Byrd, 1980; Ksir, 1981; McAuley & Leslie, 1986; McMillan, 1968), decreased index of curvature (cf. Branch & Gollub, 1974; Gollub, 1964; Howell et al., 1986; Laties & Weiss, 1966), and decreased pausing early in the interval (cf. Branch & Gollub, 1974; Howell et al., 1986; McAuley & Leslie, 1986).

The time-course of effects of cocaine on responding under FI schedules has not been reported often. Spealman et al. (1977) noted that a smaller dose of cocaine (0.27 mg/kg) increased the group average of squirrel monkeys' response rates under FI 600-s schedules across an entire session (which lasted approximately 100 minutes), whereas larger doses (0.89 and 2.68 mg/kg) increased rates early in the session, and either decreased rates or did not increase rates as much later in the session. These findings stand in contrast to the results of the current experiment in which decreases in response rates after cocaine administration, when they occurred at all, occurred at the beginning of the session, and were followed by an abrupt increase in response rates. Obvious factors that may alter time-course effects, such as species, drug, route of administration, and duration of the interval between administration and the beginning of the session, were the same in these two experiments. Other aspects were different, however. Two potentially important differences are the injection volume and maintaining event, which, in the study by Spealman et al. were 0.3 ml/kg and stimulus-shock termination, respectively. The smaller injection volume used by Spealman et al. means that the cocaine concentration in solution was higher for comparable doses measured in mg/kg of bodyweight. It is possible that the concentration of cocaine in solution can alter time-course effects, although no data exist to confirm this supposition. In addition, although the maintaining event is not usually an important determinant of the effects of acute cocaine administration (Barrett, 1976), it may alter time-course effects. Indeed, the dose-effect curves for overall response rates in the study by Spealman et al. and the present study are similar. Future research should examine the relationships between cocaine concentration and maintaining event with respect to cocaine's time-course effects.

The tolerance observed to cocaine-produced increases in response rates during this experiment is consistent with reports studying chronic d-amphetamine exposure by Branch (1979) and Tilson and Sparber (1973). However, it is inconsistent with the results of studies by Schuster et al. (1966) and Howell and Morse (1989) who did not observe tolerance. Schuster et al. (1966) reported substantial response rate-increases, and subsequent lack of tolerance development, but did so for only one subject. The present study and those by Branch (1979) and Tilson and Sparber (1977) employed larger valued FI schedules than did the study by Schuster et al. (1966). Perhaps FI schedule value is an important modulator of tolerance to stimulant drugs' rate-increasing effects (but cf. Schama & Branch, 1989). In addition, the study by Schuster at al. used a larger dose of d-amphetamine for chronic administration than did the study of Tilson and Sparber. It is also possible that the magnitude of the chronic dose helps determine tolerance to rate-increasing effects of stimulant drugs. The dose used for chronic administration in the study by Schuster et al. is not easily compared to the doses used in the study by Branch (1979), since the species of the subjects was different, or to the present experiment, since the species and drugs again were different.

There are a number of consistent differences between the procedures of Howell and Morse (1989) and studies, including the present one, which demonstrate tolerance to cocaine or d-amphetamine's response-rate-increasing effects (Branch, 1979; Tilson & Sparber, 1973). One of the most important may be the chronic dosing regimen. The chronic dosing regimen of Howell and Morse consisted of continuous infusions of cocaine for two weeks. In the other studies chronic dosing consisted of daily pre-session administration. Data presented by Reith, Benuck, and Lajtha (1987) demonstrate directly that dosing regimen may be important. These investigators compared the effects of continuous infusions with those of daily injections of cocaine on the locomotor behavior of mice. They found that continuous infusion for 18 days (25 mg/kg/day) resulted in tolerance to cocaine-produced increases in locomotion, whereas 21 intermittent injections (20.4 mg/kg/inj), occurring not less than 8 hours apart over 18 days, resulted in sensitization. The total amount of cocaine administered was approximately the same for each group. These data seem to be inconsistent with those of this study, in which intermittent injections produced tolerance, and those of Howell and Morse (1989), in which continuous infusion produced sensitization.

One way to reconcile these inconsistencies is by considering the context in which cocaine is chronically administered in relation to the behavior that is being studied. In the study by Reith at al. (1987) locomotion was always possible. Therefore, during intermittent administration, the correlation between cocaine activity and the ability to engage in the behavior studied was not perfect, and under these conditions sensitization occurred. In comparison, the study by Howell and Morse (1989) arranged availability of the behavior of interest, lever-pressing, only during daily sessions. Continuous cocaine infusion under these conditions also produced an imperfect correlation between active cocaine and the behavior studied, and sensitization occurred. During the present experiment, as during the experiment by Howell and Morse, lever-pressing was only possible during sessions. However, during the chronic-administration condition of the present experiment cocaine was not administered continuously but was injected before most sessions. Under these circumstances the correlation between active cocaine and the behavior of interest was relatively high. Tolerance occurred to cocaine-produced increases in response-rates during this experiment. Similarly, in the experiment by Reith et al., when cocaine was continuously infused the correlation between availability of the behavior studied and active cocaine was perfect, since locomotion was always possible. Under these conditions tolerance occurred. A consistent finding across these three experiments, then, is that when the correlation between cocaine administration and the availability of the behavior studied was relatively high, tolerance occurred, and when the correlation was relatively low, sensitization occurred. These consistencies support the possibility that the correlation between cocaine administration and the opportunity to engage in the behavior studied is an important modulator of tolerance.

A number of other studies support the view that the correlation between the presence of a drug and the opportunity to respond is an important determinant of that drug's chronic effects. In an early experiment, Carlton and Wolgin (1971) reported that tolerance occurred to _d_-amphetamine's anorectic effects when the drug was administered before, but not after sessions. That is, tolerance developed only when the drug's activity and the opportunity to engage in the measured behavior coincided. Similarly, Campbell and Seiden (1973) reported that tolerance to _d_-amphetamine-induced increases in rats' response rates maintained under an IRT>t schedule only occurred when the drug was administered chronically before sessions. Also, in addition to studies described previously (Branch & Sizemore, 1988; Woolverton et al., 1978) a more recent experiment by Smith (1990) underscores the importance of the context of chronic administration. Smith exposed rats to three daily sessions conducted in three different conditioning chambers. During the first session of each day nose pokes into an opening were reinforced under a Sidman avoidance procedure (Sidman, 1953), during the second session lever-presses were reinforced under an FI 5-min schedule of food presentation, and during the third session nose-key presses were reinforced under an FR 40 schedule of food presentation. When administered acutely cocaine produced dose-dependent decreases in responding under the FR and FI schedules, and increases in responding under the avoidance schedule. After the effects of acute cocaine administration were determined, one injection of cocaine (13 mg/kg) was administered daily (chronically). Cocaine was first administered chronically _after_ the last (FR 40) session for 20 days. Then cocaine was administered chronically _before_ the last session. Cocaine initially decreased responding as much as it had during acute administration, indicating that the previous 20 injections had not resulted in tolerance, and tolerance developed to this effect after 14 sessions. Cocaine was then administered daily before the second (FI 5-min) session. Cocaine again initially decreased response rates under the FI schedule as much as it did during acute administration, even though cocaine had been administered chronically by this time for over 40 consecutive sessions. Tolerance developed to this effect after 8 days. When cocaine was initially administered chronically before the avoidance session, response rates were increased as much as they had been during acute administration, again indicating that tolerance had not developed. No tolerance developed to this effect over 20 sessions. Thus, tolerance only, but not always, occurred under conditions in which cocaine was active in the presence of the behavior of interest.

In the study by Smith (1990) cocaine's activity was either perfectly negatively or positively correlated with different sessions during different chronic-administration phases of the experiment. The same is true for most studies examining this relationship (e.g., Campbell & Seiden, 1975; Carlton & Wolgin, 1971). It is unknown, therefore, to what extent the effects of intermediate levels of the contingency between drug administration and opportunity to respond would have on tolerance development. Suggestive evidence, however, does exist. Studies using morphine and other drugs (Krank et al. 1984; Mansfield & Cunningham, 1980; Siegel, 1977) have indicated that reducing the correlation between drug administration and a particular situation can retard the development of tolerance in that situation. Also, in the experiment by Howell and Morse (1989) cocaine was chronically administered in such a way that it was present in equal concentration while the subjects were in the sessions and out of the sessions. In this way, relative to the strong contingency between the presence of the drug and the experimental session in the present study and studies by Branch (1979) and Tilson and Sparber (1973), in the study by Howell and Morse the contingency was weak. This may have contributed to the lack of tolerance reported by Howell and

Morse. In addition, in the experiment by Reith (1987), since locomotion was possible at all times, the continuous infusion chronic regimen, which produced tolerance, provided a stronger contingency between locomotion and the presence of cocaine than did the intermittent injection regimen, which did not. A related issue is whether or not post-session administration would have produced tolerance in the present experiment. That is, a perfect negative correlation between cocaine's activity and opportunity to engage in the measured activity, was not studied. The present experiment consequently does not allow conclusions to be drawn about whether the tolerance observed was modulated by "physiological" and/or "behavioral" mechanisms (Chen, 1968) and is formally silent on the importance of the correlation between drug action and behavioral opportunity. Experiments comparing post-session with pre-session chronic administration certainly would be useful in this regard.

During the present experiment, when cocaine decreased responding, tolerance did not develop fully. For Subject 542 tolerance developed to the extent that reinforcement rates were maximized. This can be seen in the cumulative record for this subject (Figure 1), which shows that during acute administration (lower left record) 1.0 mg/kg cocaine increased the initial pause in the first interval to the extent that the first reinforcer was delivered more than five minutes after it became available. During chronic administration of this dose (lower left record) responding was still suppressed at the beginning of the session, but recovered enough so that reinforcers were delivered shortly after they became available. Perhaps this represents an instance where factors involving reinforcement loss and number of responses per reinforcer contribute to the outcome of chronic administration. Inspection of the mean initial pause during each interval of the session (Figure 7) is relevant in that pauses longer than the programmed interval length would necessarily decrease reinforcement rates. It can be seen that for Subject 542 acute 1.0- and 1.3- mg/kg cocaine injections produced increases in mean initial pause to the extent that the time from the beginning of the session to the first reinforcer was increased. During chronic administration the first response in this interval occurred well before food was available. Changes in cocaine-produced increases in pause duration were less systematic for the other subjects. A general observation is that increases produced by smaller doses during chronic administration were more likely to be smaller than during acute administration.

The reinforcement-loss hypothesis does not predict the tolerance to cocaine-produced increases in responding observed in this experiment. Increases in normal response rates under FI schedules do not decrease experimenter-arranged reinforcement rates. In fact, they have very little effect on reinforcement rates at all, since the interval value fixes the minimum interreinforcement interval. Branch (1979) suggested that the initial increased amount of "effort", or number of responses per reinforcer, may be important for tolerance development.

Another possible mechanism for tolerance to cocaine's response-rate-increasing effects involves an interpretation of these effects proposed by Hinrichs (1968). Hinrichs noted a similarity between the effects of novel stimuli on behavior maintained by FI schedules and the process of disinhibition in classical conditioning. In classical conditioning, a delay between the presentation of the conditional stimulus (CS) and unconditional stimulus (UCS) can result in inhibition, or reduced responding at the beginning of the CS. The presentation of novel stimuli can result in increased responding during this period, and such increases are called disinhibition. Hinrichs hypothesized that the temporal pattern of operant behavior observed under FI schedules (reduced responding at the beginning of the interval) may be an instance of (or at least analogous to) inhibition of delay. To determine if he could produce "disinhibition" Hinrichs reinforced keypecking by pigeons on an FI 60-s schedule of food delivery. After response rates and patterns became stable, the key color was changed during 6 randomly selected intervals (probes) during the 60 normally presented for four successive sessions. During probes, response rates increased early in the interval, and changed less or decreased later in the interval. During continued occasional presentations of the different key color, normal response patterns returned. When the original key color was again presented, response patterns were disrupted. Thus, the effects of novel stimuli on FI performance were similar to effects on behavior in certain classical-conditioning arrangements.

Consistent with Hinrichs' views, Ksir (1976) suggested that effects of many drugs on FI performance can be characterized as more general effects of novel stimuli. In his experiment changes in chronic administration from either saline to d-amphetamine or from d-amphetamine to saline could result in disruption of response patterning and increases in response rates under FI schedules. Thus, in this view, it is the novel-stimulus character of a drug that results in increases in response rates after initial administration, and not an effect particular to the drug itself (McKim, 1981). This interpretation has been supported using scopolamine (McKim, 1973) and cocaine (Howell et al., 1986). Howell at al. directly compared the effects of cocaine and white noise on squirrel monkeys' lever-presses maintained by an FI 5-min schedule of stimulus-shock-complex termination. Both cocaine and white noise increased response rates and decreased the duration of the initial pause. It was reported that 10 twice-per-week exposures to cocaine or white noise during one-hour sessions did not result in tolerance/habituation. This stands in contrast to what Hinrichs (1968) found when he presented a novel key color repeatedly; its effects on response patterns decreased. It is possible that repeated daily exposure to the white noise in the experiment by Howell et al. would have resulted in tolerance/habituation.

Baker and Tiffany (1985) have proposed a habituation model of morphine tolerance that is relevant to the current discussion. They derived principles from Wagner's (1979) model of habituation and applied them to morphine tolerance acquisition. In this model "representations" of a stimulus become "primed" in short-term memory with repeated presentations of the stimulus. When a representation is primed presentations of the stimulus result in less processing, and hence, less effect on behavior. Representations can also be primed by presentations of stimuli that have previously been paired with the represented stimulus. In addition, the primed representation decays over time so that repeated presentations are necessary for the priming to remain strong. Baker and Tiffany (1985) point out that this model accounts for a considerable amount of data with respect to morphine tolerance. For instance, more intermittent morphine presentations produce less tolerance because the representations are not primed often enough to counteract their decay, presentations of salient stimuli correlated with morphine administration accelerate tolerance due to priming by these stimuli, and generalization of tolerance will occur with respect to other drugs to the extent that these drugs share stimulus properties with the primed representation.

The account of tolerance development as a habituation process presented by Baker and Tiffany (1985) may be applied to the results of the present experiment. If, indeed, cocaine's rate-increasing effects on behavior maintained by FI schedules is related to the fact that cocaine is initially a novel stimulus, then one would expect habituation to this effect during repeated exposure. In the present experiment intermittent (acute) exposure did not result in as much tolerance as less intermittent (chronic) exposure. This is consistent with Baker and Tiffany's account. In addition, their view is relevant with respect to the difference in results of this experiment and that of Howell and Morse (1989), which revealed little tolerance to cocaine's rate-increasing effects. In the present experiment chronic cocaine administration was associated with a particular environmental situation, whereas in the experiment by Howell and Morse it was not. The difference in results of these two experiments is predicted by one aspect of Baker and Tiffany's formulation because stimuli differentially paired with cocaine administration would be expected to enhance habituation, or tolerance development. However, another aspect of their formulation would not predict these results. In the experiment by Howell and Morse cocaine infusion was continuous, and in the present experiment injections occurred once per day. In this respect, according to the model of Baker and Tiffany, tolerance would be expected in the study by Howell and Morse, since continuous exposure should result in more complete priming than intermittent exposure. Considering the procedures of Howell and Morse and the present experiment together, processes involving intermittency and drug-correlated stimuli are confounded. It is difficult to make predictions under these circumstances without quantitative analyses of the effects of intermittency and drug-correlated stimuli, and their interactions.

It is possible, then, to interpret the tolerance in the present experiment as habituation to the effects of a novel stimulus, cocaine, when presented repeatedly. This interpretation is supported by the findings of Hinrichs (1968) and an experiment by McKim (1981), which shows some reduction in the response-rate- increasing effects of white noise and other stimuli after repeated presentation.

The effects of saline administration during and following chronic cocaine administration in the present experiment do not support the interpretation that habituation played a role, however. If cocaine's initial effects, and subsequent tolerance, were only related to its status as a novel stimulus, then increases in response rates would be expected when saline injections replaced daily cocaine injections because administration of saline would be "novel" in the context of daily cocaine administration. The ability of a switch to saline injections to produce this effect was shown in the experiment by Ksir (1976) in which exposure to saline administration following chronic _d_-amphetamine exposure produced increases in FI-maintained response rates. In the present experiment, response rates after saline-administration probes during chronic administration were no higher than response rates after the regularly scheduled chronic dose. Because the experiment was not designed specifically to test for habituation, however, there are a number of factors that could have prevented finding increases in response rates when saline-administration probes occurred during chronic cocaine administration. These include prior exposure to many non-drug sessions during both baseline and the acute-administration phase and periodic presentations of saline and doses smaller than the chronic dose during the chronic-administration phase, all of which would serve to reduce the "novelty" of saline administration. Future experiments that keep the number of sessions under each condition before probes constant could prove instructive.

An alternative interpretation of the tolerance observed in this experiment relates to behaviors not explicitly reinforced. Intermittent schedules of food presentation can produce consistent patterns of behavior not directly reinforced (Falk, 1971). These activities, often called adjunctive behavior, tend to occur immediately following food presentation, and the opportunity to engage in them can be reinforcing (Cohen, 1975; Falk, 1966). It is possible that, in the present experiment, consistently patterned, unrecorded behaviors occurred during the beginning of the interval, when lever-press rates were low. Initial increases in lever-pressing may have interfered with these activities. Tolerance may have occurred during chronic administration due to the initial disruption in the opportunity to engage in these behaviors. This can be conceptualized as a variation of the reinforcement-loss hypothesis in that access to reinforcers other than those arranged by the experimenter may have been reduced by cocaine, and tolerance may have developed in such a way as to bring access back to non-drug levels. In order to evaluate this interpretation it would be necessary to determine if cocaine-produced increases in responding maintained by FI schedules interfere with other behavior, and that this interference is important for tolerance.

McMillan (1979) conducted an experiment that bears on the issue of whether drug-induced increases in explicitly reinforced responding can interfere with adjunctive behavior. In his experiment lever-pressing by rats was reinforced under a multiple FI 90-s FR 10 schedule of food reinforcement. A drinking tube was available in the chamber, and licks were recorded. Non-drug lever-press patterns during the FI were positively accelerated. Licking predominated at the beginning of the interval for five subjects, and continued throughout the interval, occurring simultaneously with presses, for three of the five subjects. _d_-Amphetamine reliably increased lever-press rates under the FI. The same doses that increased lever-press rates decreased licking. It is possible that the decreased licking was a direct result of competition from the increased lever-pressing even though the two activities could occur simultaneously since the lever was within reach of the drinking tube. It is also possible that the decreased licking was a direct result of drug injection, so these results are not conclusive. The results are, however, consistent with the view that behavior maintained by other reinforcers early in the FI schedules can be reduced when FI rates increase.

Bacotti (1979) reported an experiment that also addresses the issue of whether increases in responding under FI schedules can interfere with other behavior, in this case explicitly reinforced other behavior. Pigeons' keypecks were reinforced according to a concurrent schedule that arranged reinforcers according to an FI schedule on one key, and an FR 50 schedule on the other. The values of the FI schedule were 1.5, 4, and 10 min during different portions of the experiment. Both schedules were operative simultaneously and independently. Under non-drug conditions responding predominated on the FR schedule during the early portions of each FI. Responding shifted to the FI schedule later in the interval. Cocaine administration increased overall FI responding and decreased FR responding. However, local rates of responding, or response rates while responding on a particular schedule, were not affected. The change in overall rates was due to an increase in time spent responding on the FI schedule. Since cocaine did not directly affect local rates of responding, it is more likely that its effects on overall rates were produced by an interaction of its effects on responding under both schedules.

The experiments by McMillan (1979) and Bacotti (1979) support the proposition that cocaine-induced increases in responding on FI schedules may reduce the frequency of other ongoing behavior. An investigation of the effects of chronic cocaine administration in such a situation, perhaps comparing concurrent variable-ratio (VR) FI schedules with concurrent variable-interval (VI) FI schedules, allowing varying degrees of initial disruption in reinforcement rates, would be informative.

An experiment by Moore and Thompson (1978), described earlier, does not support the interpretation that cocaine tolerance in this experiment was modulated by disruption of other behavior. These experimenters did not find tolerance to cocaine-produced decreases in pigeons' schedule-induced (ie., adjunctive) responding on a mirror. Although responding on the mirror occurred during EXT components, and not at the beginning of FI schedules, the findings suggest that cocaine tolerance may not occur with certain classes of schedule-induced behavior. It should be noted, however, that a chronic dose was used that initially decreased the reinforced keypecking. In the present experiment, the chronic dose initially increased lever-pressing. It is possible that the dose used in the present experiment was functionally smaller with respect to schedule-induced behaviors. In fact, the doses used may have had little effect on these behaviors except indirectly by increasing rates of lever-pressing. Clearly, more experimentation is required on the effects of chronic cocaine administration on concurrent activities, both schedule-induced and directly reinforced behavior.

Another interpretation of tolerance to cocaine's response-rate-increasing effects on behavior maintained by FI schedules also relies on behavior not explicitly reinforced. Repeated cocaine administration has been shown to produce sensitization in a number of contexts (Post &

Kopanda, 1976). For instance, Tatum and Seevers (1929) reported increased grooming in a rhesus monkey after repeated cocaine administration. It is possible that, with respect to the present experiment, decreases in lever-press rates that occurred after repeated cocaine administration were related to increased effects on other behavior in the chamber. For instance, repeated cocaine administration may have produced sensitization to cocaine's effects on grooming. The increased amount of time spent grooming may have reduced the time spent lever-pressing. Further research in which other behavior is observed, during FI schedules, under non-drug conditions and after acute and chronic cocaine administration would be useful. Increases in the amount of other behavior, with respect to non-drug control conditions, occurring simultaneously with tolerance to cocaine-produced increases in response rates under the FI schedule, would constitute support for this interpretation.

SUMMARY AND GENERAL CONCLUSIONS

While the effects of acute cocaine administration and other stimulants on performance under FI schedules have been well studied, the effects of repeated administration have not. In the present experiment, repeated cocaine administration resulted in a reduction of cocaine's response-rate-increasing effects on squirrel monkeys' responding under FI schedules of food reinforcement. In two of the four subjects this tolerance was characterized by a general shift in the effects of cocaine from smaller to larger doses, when effects across the interval and session are considered. In the remaining two subjects tolerance was characterized by a general "flattening" of the dose-effect function so that the effects of the chronic doses and all larger doses studied came to resemble control performances. These results are generally consistent with those of other experiments that have administered cocaine (Branch, 1979) and _d_-amphetamine (Tilson & Sparber, 1973) chronically before sessions. In an experiment that did not show tolerance (Howell & Morse, 1989) cocaine was administered continuously for two weeks during the chronic-administration phase. Other research suggests that the way in which drugs are administered chronically can affect tolerance. It is possible that tolerance was observed in this experiment and those of Branch (1979) and Tilson and Sparber (1973), in part, because there was a strong contingency between when the drug was active and the opportunity to respond.

The present experiment does not distinguish between "behavioral" and "physiological" tolerance development (cf. Chen, 1968). Experiments comparing the effects of cocaine administered chronically after sessions with the effects of pre-session administration would be helpful.

The present research implicates as possible behavioral mechanisms of tolerance cocaine's initial increase in the number of responses per reinforcer, habituation to cocaine's effects as a "novel" stimulus, cocaine's initial disruption of schedule-induced behavior toward the beginning of the intervals, and other behavior becoming sensitized to cocaine's effects and interfering with lever-pressing. Future research should help to distinguish among these possibilities.

REFERENCES

Bacotti, A.V. (1979). Effects of cocaine and morphine on concurrent schedule-controlled performances. Journal of Pharmacology and Experimental Therapeutics, 212, 280-286.

Baker, T.B. & Tiffany, S.T. (1985). Morphine tolerance as habituation. Psychological Review, 92, 78-108.

Barrett, J.E. (1976). Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. Journal of Pharmacology and Experimental Therapeutics, 196, 605-615.

Branch, M.N. (1979). Consequent events as determinants of drug effects on schedule controlled behavior: Modification of effects of cocaine and d-amphetamine following chronic amphetamine administration. Journal of Pharmacology and Experimental Therapeutics, 210, 354-360.

Branch, M N. (1984). Rate dependency, behavioral mechanisms, and behavioral pharmacology. Journal of the Experimental Analysis of Behavior, 42, 511-522.

Branch, M.N. (1990). Cocaine tolerance: Interactions among random-ratio and random-interval reinforcement-schedule parameters and repeated exposure to cocaine. Drug Development Research, 20, 19-30.

Branch, M.N. & Dearing, M.E. (1982). Effects of acute and daily cocaine administration on performance under a delayed-matching-to-sample procedure. Pharmacology, Biochemistry and Behavior, 16, 713-718.

Branch, M.N. & Gollub, L.R. (1974). A detailed analysis of d-amphetamine on behavior under fixed-interval schedules. Journal of the Experimental Analysis of Behavior, 21, 519-539.

Branch, M.N., & Sizemore, G.M. (1988). Behavioral tolerance to cocaine in squirrel monkeys: Acute and chronic effects on complex operant behavior. Pharmacology Biochemistry & Behavior, 30, 737-748.

Byrd, L.D. (1979). The behavioral effects of cocaine: Rate dependency or rate constancy. European Journal of Pharmacology, 56, 355-362.

Campbell, J.C. & Seiden, L.S. (1973). Performance influence on the development of tolerance to amphetamine. Pharmacology, Biochemistry and Behavior, 1, 703-708.

Carey, R.J. & Kritkausky, R.P. (1972). Absence of a response-rate-dependent effect of d-amphetamine on a DRL schedule when reinforcement is signalled. Psychonomic Science, 26, 285-286.

Carlton, P.L. & Wolgin, D.L. (1971). Contingent tolerance to the anorexigenic effects of amphetamine. Physiology and Behavior, 7, 221-223.

Chen, C-S (1968). A study of the alcohol tolerance effect and an introduction of a new behavioral technique. Psychopharmacologia, 12, 433-440.

Cohen, I.L. (1975). The reinforcement value of schedule-induced drinking. Journal of the Experimental Analysis of Behavior, 23, 37-44.

Crowell, C.R., Hinson, R.E., & Siegel, S. (1981). The role of conditional drug responses in tolerance to the hypothermic effects of ethanol. Psychopharmacology, 73, 51-54.

Dews, P.B. (1955). Studies on behavior I: Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. The Journal of Pharmacology and Experimental Therapeutics, 113, 393-401.

Dews, P.B. (1958). Analysis of effects of psychopharmacological agents in behavioral terms. Federation Proceedings, 17, 1024-1030.

Dollard, J. & Miller, N.E. (1950). Personality and Psychotherapy. New York:McGraw-Hill.

Downs, A.W. & Eddy, N.B. (1932). The effect of repeated doses of cocaine on the rat. The Journal of Pharmacology and Experimental Therapeutics, 46, 199-200.

Falk, J.L. (1966). The motivational properties of schedule-induced polydipsia. Journal of the Experimental Analysis of Behavior, 9, 19-25.

Falk, J.L. (1971). The nature and determinants of adjunctive behavior. Physiology and Behavior, 6, 577-588.

Foree, D.D., Moretz, F.H., & McMillan, D.E. (1973). Drugs and punished responding II: d-amphetamine-induced increases in punished responding. Journal of the Experimental Analysis of Behavior, 20, 291-300.

Fry, W., Kelleher, R.T., & Cook, L. (1960). A mathematical index of performance on fixed-interval schedules of reinforcement. Journal of the Experimental Analysis of Behavior, 3, 193-199.

Gollub, L.R. (1964). The relations among measures of performance on fixed-interval schedules. Journal of the Experimental Analysis of Behavior, 7, 337-343.

Grabowski, J. & Dworkin, S.I. (1985). Cocaine: an overview of current issues. The International Journal of the Addictions, 20, 1065-1088.

Hake, D.F. & Azrin, N.H. (1963). An apparatus for delivering pain shock to monkeys. Journal of the Experimental Analysis of Behavior, 6, 297-298.

Hinrichs, J.V. (1968). Disinhibition of delay in fixed-interval instrumental conditioning. Psychonomic Science, 12, 313-314.

Hoffman, S.H., Branch, M.N., & Sizemore, G.M. (1987). Cocaine tolerance: Acute versus chronic effects as dependent on fixed-ratio size. Journal of the Experimental Analysis of Behavior, 47, 363-376.

Howell, L.L., Byrd, L.D., & Marr, M.J. (1986). Similarities in the rate-altering effects of white noise and cocaine. Journal of the Experimental Analysis of Behavior, 46, 381-394.

Howell, L.L. & Morse, W.H. (1989). Behavioral effects of chronically administered cocaine in squirrel monkeys. Psychopharmacology, 97, 12-16.

Hughes, C.E. & Branch, M.N. (1991). Tolerance to and residual effects of cocaine in squirrel monkeys depend on reinforcement-schedule parameter. Journal of the Experimental Analysis of Behavior, 56, 345-360.

Johanson, C-E. & Fischman, M. W. (1989). The pharmacology of cocaine related to its abuse. Pharmacological Reviews, 41, 3-52.

Kelleher, R.T. & Morse, W.H. (1964). Escape behavior and punished behavior. Federation Proceedings, 23, 808-817.

Krank, M.D., Hinson, R.E., & Siegel, S. (1984). Effect of partial reinforcement on tolerance to morphine-induced analgesia and weight loss in the rat. Behavioral Neuroscience, 98, 72-78.

Ksir, C. (1976). Rate dependent drug effects: Possible state dependency. Pharmacology Biochemistry & Behavior, 4, 165-168.

Ksir, C. (1981). Rate-convergent effects of drugs. In T. Thompson, P.B. Dews, & W.A. McKim (Eds.), Advances in Behavioral Pharmacology (Vol. 3, pp. 39-59). New York: Academic Press.

Laties, V.G. & Weiss, B. (1966). Influence of drugs on behavior controlled by internal and external stimuli. Journal of Pharmacology and Experimental Therapeutics, 152, 388-396.

Mansfield, J.G. & Cunningham, C. (1980). Conditioning and extinction of tolerance to the hypothermic effect of ethanol in rats. Journal of Comparative and Physiological Psychology, 94, 962-969.

McAuley, F. & Leslie, J.C. (1986). Molecular analyses of the effects of d-amphetamine on fixed-interval schedule performances of rats. Journal of the Experimental Analysis of Behavior, 45, 207-219.

McKim, W.A. (1973). The effects of scopolamine on fixed-interval behavior in the rat: a rate-dependency effect. Psychopharmacologia, 32, 255-264.

McKim, W.A. (1981). Rate-dependency: a nonspecific behavioral effect of drugs. In T. Thompson, P.B. Dews, & W.A. McKim (Eds.), Advances in Behavioral Pharmacology (Vol. 3, pp. 61-73). New York: Academic Press.

McMillan, D.E. (1968). The effects of sympathomimetic amines on schedule-controlled behavior in the pigeon. The Journal of Pharmacology and Experimental Therapeutics, 160, 315-325.

McMillan, D.E. (1973). Drugs and punished responding I: Rate-dependent effects under multiple schedules. Journal of the Experimental Analysis of Behavior, 19, 133-145.

McMillan, D.E. (1979). Effects of d-amphetamine and caffeine on schedule-controlled and schedule-induced responding. Journal of the Experimental Analysis of Behavior, 32, 445-456.

McMillan, D.E. & Healey, M.L. (1976). Some effects of d-amphetamine and pentobarbital on performance under a long fixed-interval schedule. Journal of the Experimental Analysis of Behavior, 25, 389-399.

Moore, M.S. & Thompson, D.M. (1978). Acute and chronic effects of cocaine on extinction-induced aggression. Journal of the Experimental Analysis of Behavior, 29, 309-318.

Post, R.M. & Kopanda, R.T. (1976). Cocaine, kindling, and psychosis. American Journal of Psychiatry, 133, 627-634.

Post, R.M. & Rose, H. (1976). Increasing effects of repetitive cocaine administration in the rat. Nature, 260, 731-732.

Reith, M.E.A., Benuck, M., & Lajtha, A. (1987).Cocaine disposition in the brain after continuous or intermittent treatment and locomotor stimulation in mice. The Journal of Pharmacology and Experimental Therapeutics, 243, 281-287.

Schama, K.F. & Branch, M.N. (1989). Tolerance to effects of cocaine on schedule-controlled behavior: Effects of fixed-interval schedule parameter. Pharmacology Biochemistry and Behavior, 32, 267-274.

Schuster, C R., Dockens, W.S., & Woods, J.H. (1966). Behavioral variables affecting the development of tolerance. Psychopharmacologia, 9, 170-182.

Sidman, M. (1953). Two temporal parameters of the maintenance of avoidance behavior. Journal of Comparative and Physiological Psychology, 46, 253-261.

Siegel, S. (1977). Morphine tolerance acquisition as an associative process. Journal of Experimental Psychology: Animal Behavior Processes, 3, 3-13.

Siegel, S. (1978). Tolerance to the hyperthermic effect of morphine in the rat is a learned response. Journal of Comparative and Physiological Psychology, 92, 1137-1149.

Skinner, B.F. (1948). Walden two. New York: MacMillan.

Skinner, B. F. (1953). Science and human behavior. New York: Macmillan.

Skinner, B. F. (1957). Verbal behavior. Englewood Cliffs, NJ: Prentice-Hall.

Smith, J.B. (1990). Situational specificity of tolerance to decreased operant responding by cocaine. Pharmacology Biochemistry and Behavior, 36, 473-477.

Spealman, R.D., Goldberg, S.R., Kelleher, R.T., Goldberg, D.M., & Charlton, J.P. (1977). Some effects of cocaine and two cocaine analogs on schedule-controlled behavior of squirrel monkeys. Journal of Pharmacology and Experimental Therapeutics, 202, 500-509.

Tatum, A.L. & Seevers, M.H. (1929). Experimental cocaine addiction. The Journal of Pharmacology and Experimental Therapeutics, 36, 401-410.

Thompson, D.M. (1977). Development of tolerance to the disruptive effects of cocaine on repeated acquisition and performance of response sequences. Journal of Pharmacology and Experimental Therapeutics, 203, 294-302.

Thompson, D.M. & Moerschbaecher, J.M. (1979). An experimental analysis of the effects of d-amphetamine and cocaine on the acquisition and performance of response chains in monkeys. Journal of the Experimental Analysis of Behavior, 32, 433-444.

Tilson, H.A. & Sparber, S.B. (1973). The effects of d- and l-amphetamine on fixed-interval and fixed-ratio behavior in tolerant and nontolerant rats. The Journal of Pharmacology and Experimental Therapeutics, 187, 372-379.

Wagner, A.R. (1979). Habituation and Memory. In A. Dickinson and R.A. Boakes (Eds.) Mechanisms of learning and motivation (pp. 53-82). Hillsdale, NJ: Erlbaum.

Walter, D.E. & Palya, W.L. (1986). Document Set for Experiment Controllers with ECBasic or ECL Prom Sets, William L. Palya, Jacksonville, Alabama.

Wenger, G.R. (1980). Cumulative dose-response curves in behavioral pharmacology. Pharmacology Biochemistry & Behavior, 13, 647-651.

Wilson, M.C. & Brenkert, P. (1978). Effect of chronic cocaine treatment on limited access food consumption. Communications in Psychopharmacology, 2, 327-332.

Woolverton, W.L., Kandel, D. & Schuster, C.R. (1978a). Effects of repeated administration of cocaine on schedule-controlled behavior of rats. Pharmacology, Biochemistry and Behavior, 9 327-337.

Woolverton, W.L., Kandel, D. & Schuster, C.R. (1978b). Tolerance and cross-tolerance to cocaine and d-amphetamine. Journal of Pharmacology and Experimental Therapeutics, 205, 525-535.

Woolverton, W.L. & Kleven, M.S. (1988). Evidence for cocaine dependence in monkeys following a prolonged period of exposure. Psychopharmacologia, 94, 288-291.

BIOGRAPHICAL SKETCH

Kevin Francis Schama graduated from Neshaminy Senior High School, in Bucks County, Pennsylvania, in 1977. He began attendance at Bucks County Community College in 1978, and transferred to Temple University in 1980. Kevin majored in psychology at Temple University and was awarded a Bachelor of Arts and Sciences degree in May, 1983. Kevin began graduate school at the University of Florida in 1984, and obtained a Master of Science degree in psychology in 1988. Kevin continued attendance in graduate school at the University of Florida and obtained a Doctor of Philosophy degree in May, 1992. He began employment as a Research Associate in the Behavioral Biology Division of the Yerkes Regional Primate Institute at Emory University in 1992.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Marc N. Branch

Marc N. Branch, Chairman
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Edward F. Malagodi

Edward F. Malagodi
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Brian A. Iwata

Brian A. Iwata
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Donald J. Stehouwer

Donald J. Stehouwer
Associate Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Wm D Wolking

William D. Wolking
Professor of Special Education

This dissertation was submitted to the Graduate Faculty of the Department of Psychology in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May, 1992

____
Dean, Graduate School